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SEMINAR TOPICS

CHEMISTRY 435

I Semester 1954-55

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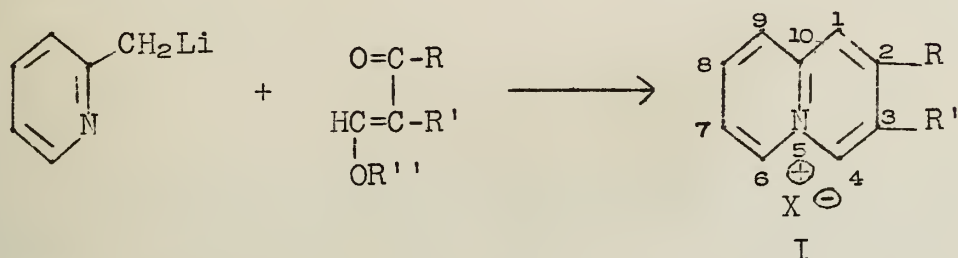
THE QUINOLIZINIUM ION AND SOME OF ITS DERIVATIVES

Reported by Harvey M. Loux

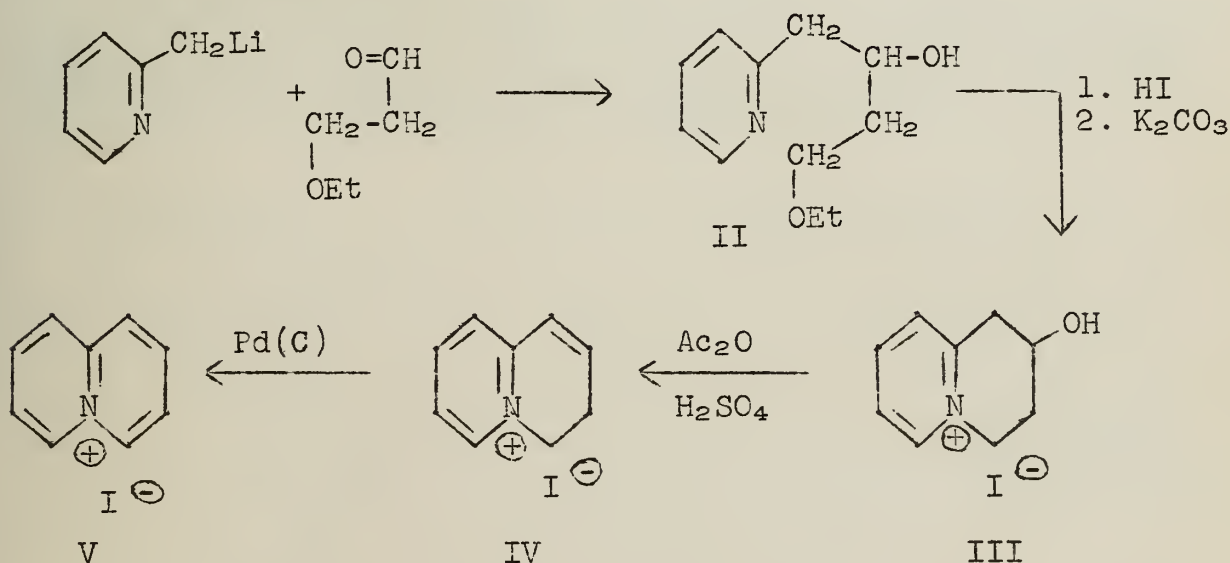
September 24, 1954

The quinolizinium ion was first proposed and proved conclusively in 1949 by Woodward and coworkers^{1,2} to be a constituent of the alkaloid sempervirine.

Several investigators^{2,3,4} have synthesized quinolizinium salts substituted in positions 2 and 3 (I) by the following procedure:



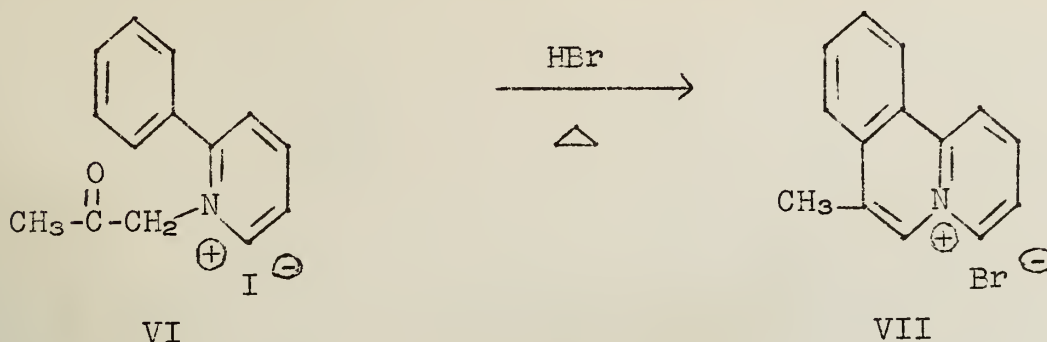
This method gives very poor yields for the unsubstituted salts. Boekelheide and Gall⁵, however, have recently developed a good synthetic procedure by which quinolizinium iodide may be obtained in fair yields.



The quinolizinium iodide is quite soluble in water and is readily transformed into perchlorate and picrate salts. It absorbs five moles of hydrogen catalytically to form quinolizidine. The structure of the carbinol (III) was established by reduction to 2-hydroxyquinolizidine followed by oxidation to 2-quinolizidone. This was identified as the picrate, previously described.

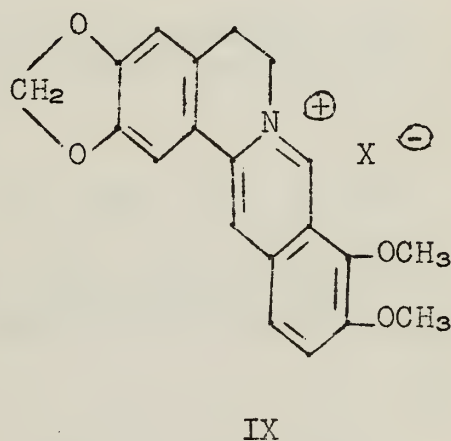
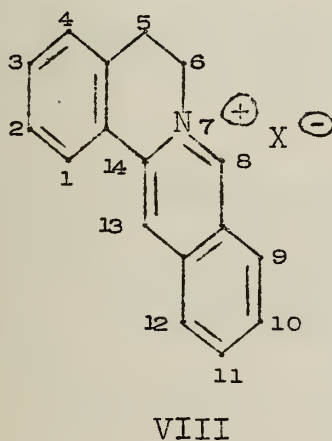
Quite recently Bradsher and Beavers⁶ have reported the synthesis of benzoquinolizinium salts by methods of aromatic cyclodehydration. These methods eliminate the necessity for dehydrogenation and are well suited for the synthesis of compounds which are sensitive to high temperatures. By treating α -phenylpyridine with α -iodoacetone they obtained N-acetyl- α -phenylpyridinium iodide (VI). Heating under reflux with 48%

hydrobromic acid for fifty-one hours brought about ring closure to 7-methylbenzo[a]quinolizinium bromide (VII) in 75% yield.

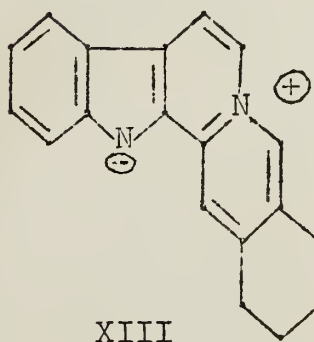
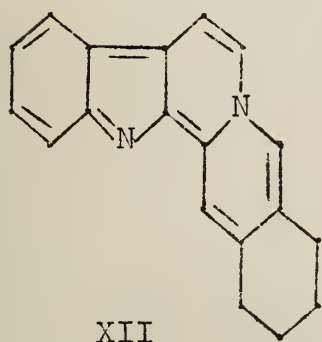
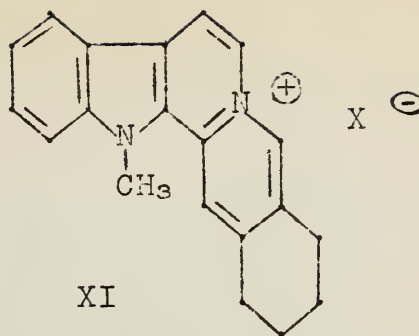
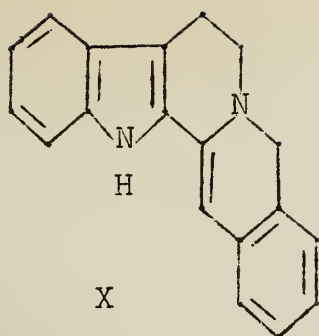


Oxidation of VII with permanganate to give phthalic acid together with ultraviolet absorption studies provided evidence supporting the structure suggested. By using phenacyl bromide in place of α -iodoacetone, the phenyl-substituted benzoquinolizinium salt was obtained in 42% yield. Since the phenacyl salt has a lower cyclization rate than the acetyl salt⁷ this reaction required fourteen days for completion.

The protoberberine alkaloids contain the dibenzodihydroquinolizinium skeleton (VIII) with methoxy, methylenedioxy, and hydroxy substituents on positions 2, 3, 9, and 10. Included among the more common of these alkaloids are berberine⁸ (IX), columbamine^{8,9}, coptisine^{8,10}, and palmatine^{8,11}.



The alkaloid sempervirine was assigned structure X by Prelog¹² in 1948 on the basis of degradative studies. In 1949 Woodward and Witkop¹ suggested structure XII as being in better agreement with the color and with the fact that the infrared absorption spectrum of sempervirine contains no N-H band, whereas all N-unsubstituted indoles have a sharp peak at 2.9 μ . The ionic structure (XIII) containing the quinolizinium ion would contribute an important part to the actual configuration of sempervirine. This fact makes understandable the formation of metho-salts of structure XI as well as the color and high basicity of the alkaloid.



At about the same time Woodward and McLamore² carried out a synthesis of sempervirine methochloride which confirmed their proposed structure. The reaction was a condensation of N-methylharman (from N-methyltryptophane) with isopropoxymethylenecyclohexanone in a manner similar to that given for the preparation of I.

Schwyzer¹³ has reported a method for transforming an alkaloid of the yohimbine type into one of the sempervirine type.

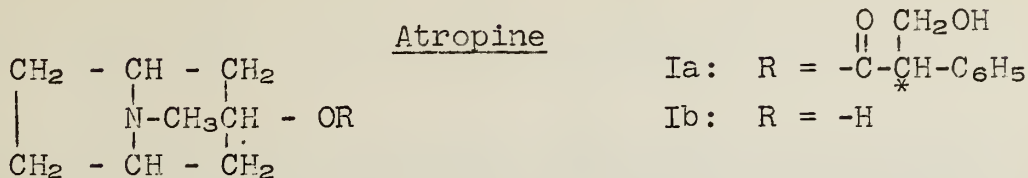
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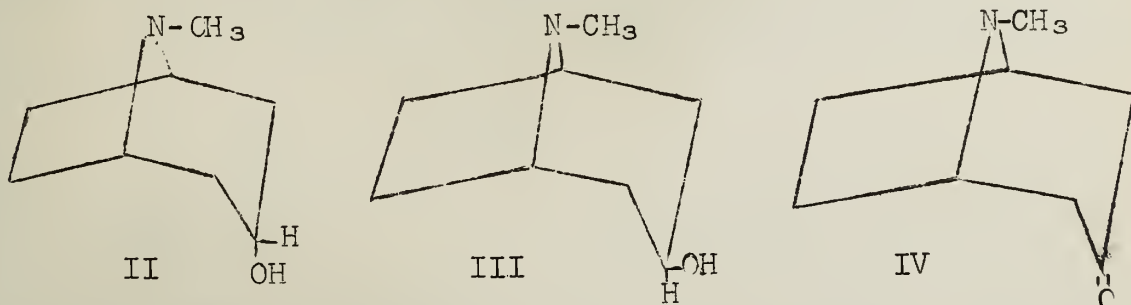
THE STEREOCHEMISTRY OF ATROPINE AND COCAINE

Reported by H. E. Knipmeyer

September 24, 1954



Atropine (Ia) has been shown to be an ester of tropic acid and the amino alcohol tropine (Ib).¹ Two geometrical isomers of tropine should be capable of existence. Their three-dimensional formulae are shown in structures II and III.

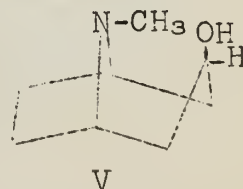


The isomer of tropine, pseudotropine, was prepared by Willstaetter² by the reduction of tropinone (V) under basic conditions. Tropine may be epimerized to pseudotropine in the presence of base, but the reverse is possible only by oxidation to the ketone followed by reduction with zinc dust and hydriodic acid.^{2,3} Tropinone may also be selectively reduced by LiAlH_4 to pseudotropine.⁴

The acid-catalyzed stereospecific migration of acyl groups⁵ from nitrogen to oxygen and the reverse migration under the influence of dilute alkali has been applied by Fodor to elucidate the configuration of the hydroxyl group relative to that of the nitrogen bridge. Fodor and Nador,⁶ whose work has been confirmed by Fieser,⁷ found that N-benzoylnorpseudotropine was transformed into O-benzoylnorpseudotropine by acid and that the reverse reaction took place when the O-benzoyl compound was treated with alkali. In contrast to this the epimeric nortropine analogs gave no reaction under identical conditions.

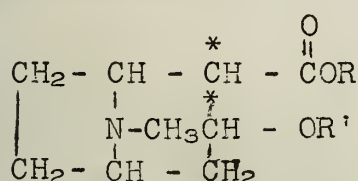
From this work it is evident that norpseudotropine (and analogously the N-methyl compounds) must have the nitrogen atom and the hydroxyl group in an α - or cis- relationship to one another in order to permit the existence of the cyclic intermediate involved in the rearrangement. Thus, structure II may be assigned to tropine and structure III to the epimeric pseudotropine.

An additional problem is whether the piperidine ring exists in the boat (V) or chair (III) form. It is difficult to predict which form of the piperidine ring is better in the bicyclic system under discussion for a chair conformation of the piperidine ring would necessitate a boat form for the cycloheptane ring. However the evidence seems to favor the chair conformation.

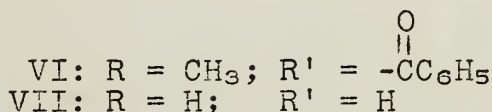


Sparke⁸ has interpreted the base-catalyzed epimerization of tropine to pseudotropine and the selective reduction of tropinone to the pseudo isomer in terms of the concept of axial and equatorial bonds⁹ and has concluded that pseudotropine should have an equatorial hydroxyl group as this configuration is known to be the more stable one. Since it has been shown that the hydroxyl group must be cis to the nitrogen bridge, this would mean that the chair form of the piperidine ring would be the more favored.

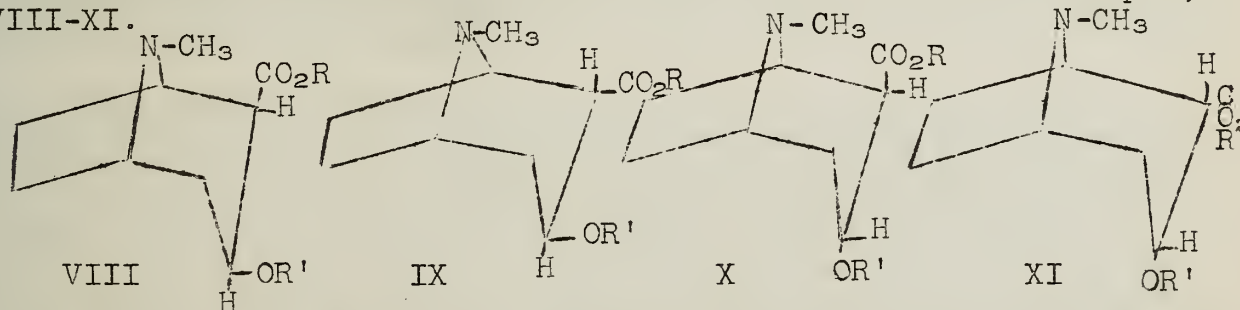
It was found that benzoylpseudotropine was hydrolyzed approximately 39.5 times as fast as was benzoyltropine.¹⁰ Although this was interpreted to mean that the piperidine ring is in the boat conformation and that the nitrogen bridge and the hydroxyl group are cis in tropine (the reverse of the true configuration), these data are explained by the recent work of Barton¹¹ who found that esters having an axial hydroxyl group are less readily hydrolyzed than those having the equatorial configuration.



Cocaine



Cocaine¹ (VI) is an ester which is hydrolyzed to benzoic acid, methanol and the amino alcohol ecgonine (VII). The introduction of the carboxyl group into the tropine residue permits the existence of four diastereoisomers and their enantiomorphs, VIII-XI.



Einhorn and Marquardt¹² observed that ecgonine on treatment with alkali is converted to a diastereoisomer which is now called pseudoecgonine. The similarity of this and the previously discussed tropine-pseudotropine interconversion suggests that this change is due to epimerization of the C-3 hydroxyl group. This idea has been shown to be erroneous by Findlay¹³ who gives evidence that the ecgonine-pseudoecgonine transformation involves epimerization of the C-2 carboxyl group rather than the C-3 hydroxyl. It is known that α -hydrogen atoms of esters are more acidic than those of carboxylate anions.¹⁴ It has been shown¹⁵ that cocaine is converted into pseudoecgonine in 54% yield by base whereas ecgonine gives only 2% of the pseudo isomer under identical conditions. It is significant that ecgonine methyl ester gives on treatment with methyl iodide a methiodide which is identical with that obtained from pseudoecgonine methyl ester.¹⁶ Here the presence of the quaternary ammonium pole would aid epimerization at C-2.

The relationship between the hydroxyl group and the carboxyl group in ecgonine and pseudoecgonine has been determined.¹⁷ Curtius degradation of the carboxyl group of ecgonine gave an amine whose N-benzoyl derivative underwent reversible acyl

migration to the C-3 oxygen atom. LiAlH_4 reduction of cocaine gave ecgoninol which formed a cyclic benzylidene acetal. Analogous transformations failed to proceed in the pseudoecgonine series. Thus it is shown that in ecgonine the substituents at C-2 and C-3 are cis to one another. In a further application of the method of acyl migration Fodor found that N-acetylnorpseudoecgonine rearranged in the presence of acid to the O-acetyl derivative and that this reaction could be reversed by the addition of alkali. He therefore assigned structure IX to pseudoecgonine. As he was unable to observe the same reaction with the norecgonine compounds and did not consider that the ecgonine-pseudoecgonine epimerization was due to a change at C-2, he assigned structure XI to ecgonine. In contrast to this work, Findlay¹³ found that O-benzoylnorecgonine undergoes ready acyl migration in dilute potassium carbonate solution and that this reaction may be reversed by acid. Thus it was shown that the C-3 hydroxyl and the nitrogen bridge must be cis to each another. Ecgonine must then have structure VIII. In agreement with Fodor's Fodor's assignment, pseudoecgonine is IX.

Additional evidence in favor of the above choice of configurations is to be found in the work of Willstaetter¹⁸ who observed that ecgonine methyl ester methiodide underwent the Hofmann degradation rapidly to yield a cycloheptatriene carboxylic acid and dimethylamine while the analogous compound derived from pseudoecgonine decomposed at a much slower rate. It has been shown by English workers¹⁹ that such a reaction is probably E2 in nature. From structure VIII it is seen that in ecgonine the nitrogen bridge and the hydrogen attached to the C-2 carbon bear a trans relationship to each other and thus fulfill the requirement for such an elimination.

That cocaine is indeed represented by structure VIII and pseudococaine by IX is confirmed by work recently published by Fodor and coworkers²⁰. Cocaine and pseudococaine were converted to two epimeric 2-methyl-3-tropinones. The fact that two epimeric ketones were obtained affords proof that cocaine and pseudococaine differ only in the configuration at C-2. The cis relationship of the nitrogen bridge and the carboxyl group in cocaine was shown by the conversion of ecgonine to N-carbamylnorecgonine which forms a cyclic urea derivative.

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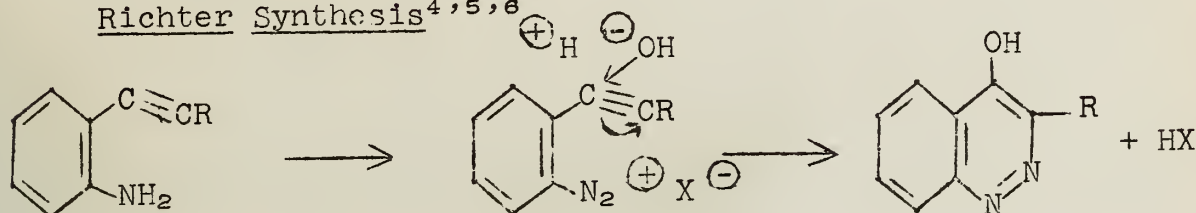
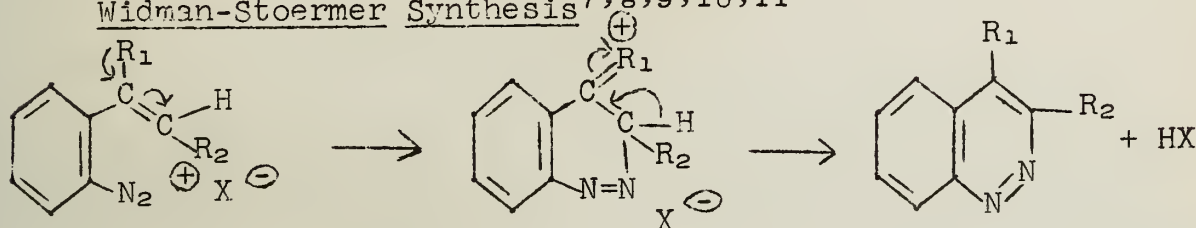
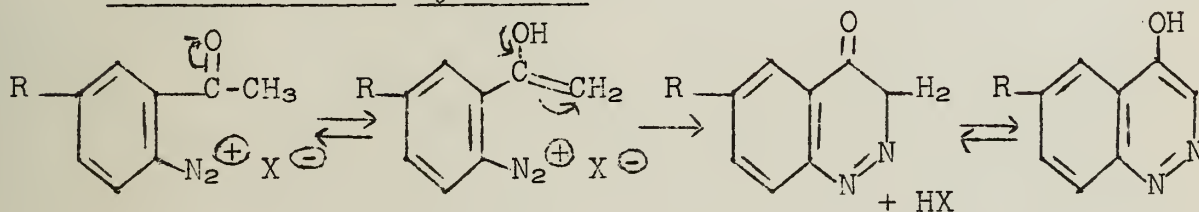
RECENT DEVELOPMENTS IN THE CHEMISTRY OF CINNOLINE DERIVATIVES

Reported by Roger H. Kottke

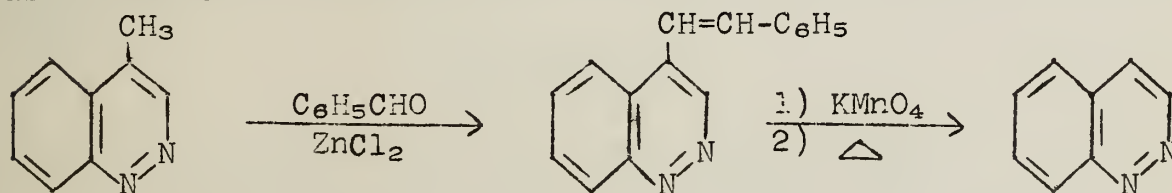
October 1, 1954

SYNTHESES

The three main routes to cinnoline derivatives are shown here. Other methods are known^{2,28}, but their applicability is not as general.

Richter Synthesis^{4,5,6}Widman-Stoermer Synthesis^{7,8,9,10,11} $R_1 = C_6H_5, CH_3$ $R_2 = C_6H_5, \text{Alkyl}$ Borsche-Herbert Synthesis^{1,12} $R = CN, NO_2, Cl$

The best method for the preparation of cinnoline itself is as follows:¹³

REACTIONS

Cinnolines are usually yellow solids. They are fairly weak bases¹⁵, generally forming stable salts. It has been shown that the basic center of these compounds is N_1 ¹⁶. The reactions of the 4-substituted cinnolines are the most characteristic of this class of compounds and are worthy of consideration.

Oxidation

Cinnolines behave in a manner similar to quinolines on oxidation; the benzene ring is attacked in preference to the heterocyclic ring. Benzo [c] cinnoline, when treated with potassium permanganate, gives pyridazine- 3,4,5,6-tetracarboxylic acid¹⁴.

Reduction

Very little has been done on the reduction of cinnolines, but both 1,2-dihydro- and 1,2,3,4-tetrahydrocinnolines are known. When 4-phenylcinnoline (I) is treated with zinc and ammoniacal alcohol 4-phenyl-1,2-dihydrocinnoline is formed in good yield, which on catalytic reduction is converted to 4-phenyl-1,2,3,4-tetrahydrocinnoline. However, when I is treated with zinc and acetic acid, 3-phenylindole is formed²¹. Other 4-substituted cinnolines give similar results with sodium and alcohol²².

Reactions of 4-methylcinnolines

If N₁ is the basic center in cinnolines, then 4-methylcinnoline would be expected to react with aldehydes as do quinaldine and lepidine. Reaction of 4-methylcinnolines with aldehydes has been carried out in the presence of anhydrous zinc chloride^{13,17}, and with better results by using hydrogen chloride gas¹⁸. Methyl group reactivity is enhanced by formation of the alkyl cinnolinium iodides¹⁹.

Reactions of 4-chlorocinnolines

Treatment of 4-hydroxycinnoline with a mixture of PCl₅ and POCl₃ yields 4-chlorocinnoline²³. 4-Chlorocinnoline is more reactive than 4-chloroquinoline, and its reactions are very similar. Boiling water converts it to 4-hydroxycinnoline²⁴. It forms the acetoxy compound when heated under reflux with acetic anhydride²⁵, and reacts with ammonia²⁶ and amines²⁷. Phenol and ammonium carbonate convert 4-chlorocinnoline to 4-phenoxy cinnoline²⁴, whereas 5-chloroacridine yields 5-aminoacridine on similar treatment²⁹. 4-Aminocinnoline is obtained by fusion of 4-phenoxy cinnoline with ammonium acetate²⁵. Because of the reactivity of the chlorine atom, 4-chlorocinnoline condenses with phenylacetonitrile, but attempts to condense it with enolic active methylene compounds have not been successful²⁰.

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INTERPRETATION OF ELECTROPHILIC AROMATIC SUBSTITUTION AND SOLVOLYSIS OF ALLYLIC AND BENZHYDRYL CHLORIDES IN TERMS OF HYPERCONJUGATION

Reported by Robert D. Stolor

October 1, 1954

In the interpretation of experimental data in terms of the electrical effects of substituents, three mechanisms have been postulated: (1) the direct (or field) effect, (2) the inductive effect, and (3) electron delocalization (the mesomeric and electromeric effects).¹ (1) and (2) have been discussed recently.² Electron delocalization usually involves π -type orbitals, and is the mechanism by which conjugation operates.

Conjugation, in general, has been classified as follows:³ (a) First-order conjugation includes the familiar conjugation of alternate multiple bonds or of unshared electron pairs with multiple bonds. (b) Second-order conjugation (first order hyperconjugation) is conjugation between the electrons of a single bond and those of multiple bonds. (c) Third-order conjugation (second order hyperconjugation) is electron delocalization involving only single bonds.

The molecular orbital approximation has been applied to hyperconjugation,^{3,4,5,6} and the delocalization of electrons from a methyl group into the π -orbitals of a multiple bond has been described.⁴

Extensive interpretation of physical data, equilibrium data and many types of reactions in terms of hyperconjugation have been made,⁷ but this discussion will be limited largely to the interpretation of kinetic data for the reactions cited.

ELECTROPHILIC AROMATIC SUBSTITUTION⁸

Nitration of toluene and *t*-butylbenzene at 45° in 90% aqueous acetic acid:⁹

	% Product			Relative Rates	Partial Rate Factors		
	<u>o</u>	<u>m</u>	<u>p</u>		<u>o</u>	<u>m</u>	<u>p</u>
Me ϕ	56.5	3.5	40.0	1.00	42	2.5	58
<i>t</i> -Bu ϕ	12.0	8.5	79.5	.64	5.5	4.0	75

The isomer ratio is not greatly changed when sulfuric acid is used as solvent.¹⁰

The increase in rate of meta substitution is attributed to the inductive and inductomeric effects of the substituents, giving the order: *t*-butyl > methyl > H. Assuming that steric effects are unimportant in the *m*- and *p*-positions, the *p* and *m* partial rate factors indicate that the electrical effects of Me and *t*-Bu are of the same order of magnitude. Therefore the same mechanism is probably involved for both substituents. The authors interpret the data as demonstrating control by the inductive effect at both the *m* and *p*-positions. Crawford⁶ and Baker⁷ also agree that the hyperconjugative effect is of minor importance in nitration. Their interpretation requires that the inductive effect be much greater at the *o,p*-positions than at the *m*-positions, and the unstated assumption is apparently made that C-C hyperconjugation is much less effective than C-H

hyperconjugation.

Rates and orientation for nitration in acetic anhydride at 25°?^a

	% Product			Relative Rates	Partial Rate Factors		
	<u>o</u>	<u>m</u>	<u>p</u>		<u>o</u>	<u>m</u>	<u>p</u>
ØMe	58.4	4.4	37.2	23.0	40.0	3.0	51.0
ØCH ₂ COOEt	42.0	10.6	47.4	3.66	4.62	1.16	10.41
ØCH ₂ Cl	32.0	15.5	52.5	.302	.290	.140	.951

A decrease in rate at all positions is observed when the inductive effect of the substituent is changed as above (+I to -I). The p rate decreases by a larger factor than the m rate. The partial rate factor for m substitution in ØCH₂COOEt is about the same as in benzene. This observation has been interpreted by Baker as an indication of a negligible inductive effect, and therefore the activation of the p position must arise from hyperconjugation. This interpretation permits estimation of the relative importance of the inductive and hyperconjugative effects in the nitration of toluene. Hyperconjugation appears to be responsible for about a ten-fold increase in the rate of p substitution, and is therefore the more important effect. If this is correct, then it follows that hyperconjugation is involved to about the same degree in the nitration of t-BuØ as for MeØ.

Bromination: (the rates are approximate)^e

	Partial Rate Factors		Relative Rates	Partial rate factors based on an assumed isomer distribution.
	<u>o</u>	<u>p</u>		
MeØ	120.	360.	100	
<u>t</u> -BuØ	5.4	97.2	18	

The data for bromination have been interpreted as showing increased steric and hyperconjugative effects as compared to nitration. The mechanisms of bromination are more complex than in nitration and less is known about the transition state. Therefore no reliable interpretation can be made.^{7,11,12}

SOLVOLYSIS (S_N1)

First-order rate constants at 0° and Arrhenius E values for the hydrolysis of benzhydryl chlorides, p-R-Ø-CHØCl, in 80% aqueous acetone:^{7b}

R	H	Me	Et	<u>i</u> -Pr	<u>t</u> -Bu
10 ⁶ k ₁	2.82	83.5	62.6	46.95	35.9
E	21.0	18.9	19.4	19.8	20.05 kcal/mol.

The order Me > Et > i-Pr > t-Bu > H has been interpreted as demonstrating control by hyperconjugation, because the opposite order for the alkyl groups is accepted for the inductive effect.

Relative rates of hydrolysis of allyl chlorides:¹³

Substituent	Rate		Rate
none	1.00		ca .04
2-Me	ca .5	CH ₃ CH ₂ CH ₂ Cl	
1-Me	5.67 X 10 ³		
3-Me	3.55 X 10 ³		
1-t-Bu	2.52 X 10 ³		
3-t-Bu	2.56 X 10 ³		
3- ϕ	ca 5. X 10 ⁵		
1,1-diMe	ca 8. X 10 ⁷		
3,3-diMe	ca 1.5 X 10 ⁷		

The author interprets these data as indicating the control of the reaction by hyperconjugation in the transition state. Since alkyl groups have about the same effect when in the 1-position as in the 3-position, steric acceleration and the inductive effects are not important. A methyl group in the 2-position has no significant effect. Me ~~t~~-Bu \gg H again suggests that C-H and C-C hyperconjugation can have about the same magnitude. A phenyl group in the 3-position produces an effect intermediate between those of one and two methyl groups.

The isotope effect found for CD₃ ϕ CHClMe (67% D in CH₃ group) on the rate of acetolysis supports operation of hyperconjugation in the transition state of solvolysis reactions.¹⁴

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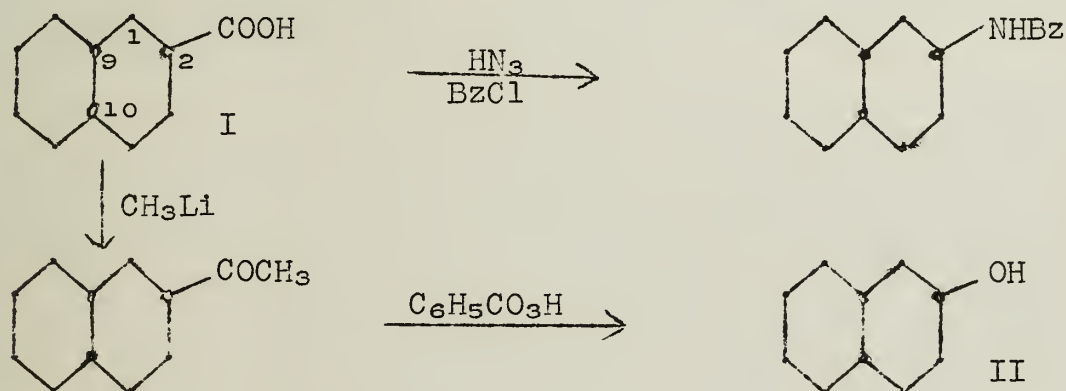
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THE DECAHYDRONAPHTHOIC ACIDS AND THEIR RELATIONSHIP
TO THE DECALOLS AND THE DECALYLAMINES

Reported by Robert J. Harder

October 8, 1954

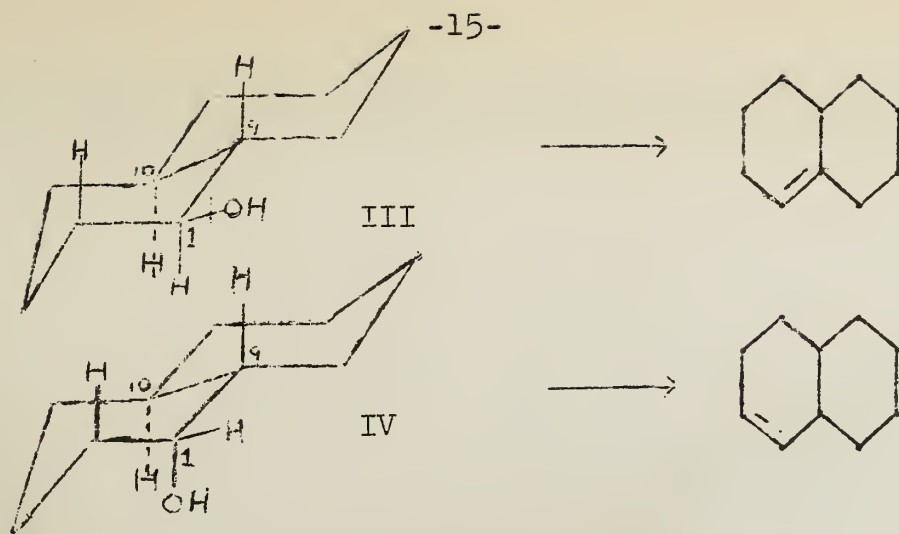
All of the possible stereoisomeric 1-decalylamines and 1-decalols have been described in the literature¹, as have all those in the 2-series. Hückel and his co-workers¹ have elucidated the configurations of these compounds along classical stereochemical lines. Since the establishment of the preferred chair conformations for the trans- and cis-decalins¹ these configurations have been reevaluated. Recent interest^{2,3} in the mechanism of the reaction of nitrous acid with alicyclic amines has led to the necessity of fixing with more certainty the configurational relationship between the reacting amines and the alcohols produced in the reaction. This has been possible in the decalin series by relating the decalols and decalylamines to the decahydronaphthoic acids. Dauben and co-workers⁴⁻⁶ have prepared at least one pure isomer of each epimeric pair of acids and have degraded each acid to an alcohol and to an amine by stereospecific processes. If, then, the stereochemistry of any one of the three related compounds can be determined, all three can be assigned the same configuration.



In this abstract, all configurational assignments are in terms of the relative positions of the hydrogen atoms at C₉, C₁₀ and C₉, C₁₀ or C₂. In planar formulas, the position of the hydrogen atom is indicated by a black dot, a dot indicating that a hydrogen atom is above the plane of the molecule. A dot is always placed at C₉.

In the main, three methods have been used by Dauben, Tweit and Mannesmann⁶ to assign steric configurations: 1) the Tschugaieff elimination (decalols), 2) conformational analysis⁷ as applied to reaction rates (decalols) and 3) catalytic hydrogenation (decahydronaphthoic acids). Also, in the 2-decalol series, infrared data⁸ give added support to the configuration assignments from chemical evidence.

The Tschugaieff elimination reaction, involving cis-related groups, with a preference for a tertiary hydrogen over a secondary hydrogen atom^{9,10}, is of use in the cis-1- and trans-1-decalols. The trans-1-decalol whose methyl xanthate yields mainly $\Delta^{1,9}$ -octalin is assigned a trans-trans configuration (III), while the trans-1-decalol which yields mostly $\Delta^{1,2}$ -octalin is assigned the trans-cis configuration (IV).

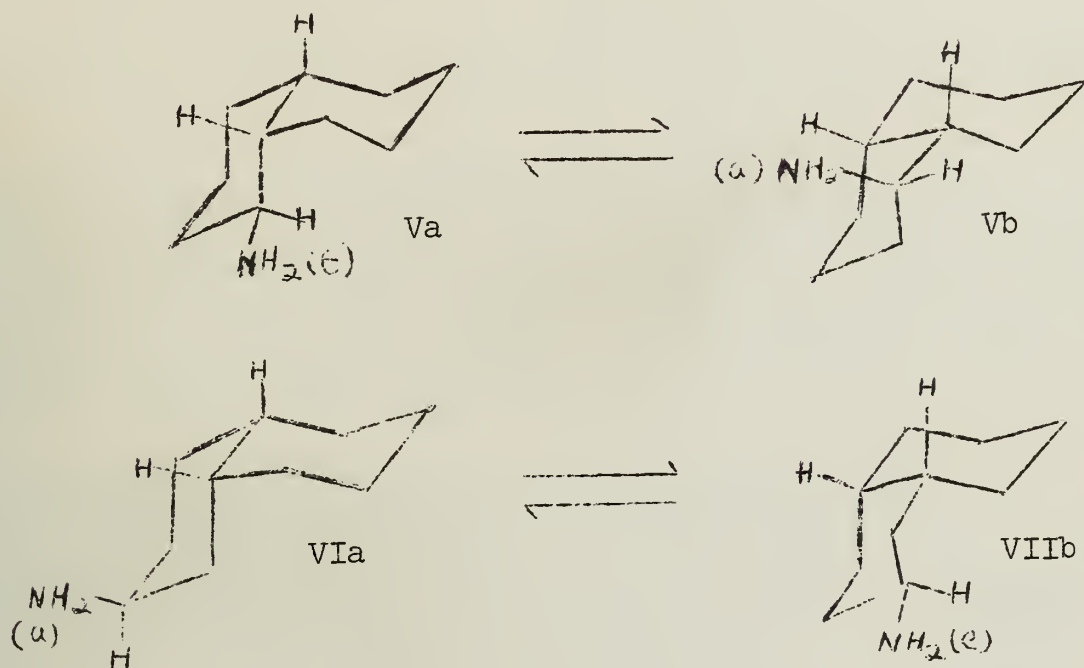


The concept of conformational analysis predicts that an epimer with an equatorial hydroxyl group is more stable than the epimer with an axial hydroxyl. Further, the epimer with equatorial hydroxyl should be more easily saponified. For example, the *trans*-2-decalol which predominates when the two epimers are equilibrated with sodium in xylene and whose acid phthalate is saponified faster by a factor of 7 is assigned the *trans-cis* configuration. In the decalin series, conformational analysis in the rigid *trans*-series is relatively clear-cut. However, in the *cis*-series, the flexibility of the ring system permits ring conversion, introducing the possibility of ambiguities of interpretation.

The third method of assigning configurations is based on the rule by Linstead and co-workers¹¹ that the predominant product formed by (rapid) catalytic hydrogenation of an aromatic acid with Adams' catalyst in acidic media has an all-*cis* configuration. The hydrogenation of 1-naphthoic acid provided a decahydronaphthoic acid which has been related to the alcohol assigned a *cis-cis* configuration on the basis of the Tschugaeff reaction, thus lending support to the assignments for both the acid and alcohol. Also, the acid (I) obtained by rapid hydrogenation of 2-naphthoic acid has been related to the alcohol (II) assigned the *cis-cis* configuration on the basis of infrared data. Thus, by using these methods, the configurations of all eight decalylamines, all eight decalols and the five known decahydronaphthoic acids have been assigned.

With these reevaluated configurations for the decalols and decalylamines, the data of Hückel and co-workers¹² may be examined with the purpose of elucidating the steric course of the reaction of nitrous acid with alicyclic amines with much greater certainty than was previously possible. It has been found, in agreement with earlier generalizations^{2,3}, that amines assigned an equatorial amino group yield alcohols with retention of configuration and that amines assigned an axial amino group yield elimination products and largely inverted alcohols. A different course of reaction takes place with *cis-trans*-1-decalylamine (Va and Vb) and *cis-trans*-2-decalylamine (VIa and VIb). From models it can be seen that V and VI are not as hindered in the rotational conformation with amino group axial as their respective epimers, *cis-cis*-1-decalylamine and *cis-cis*-2-decalylamine, and therefore it is not

surprising that they yield, besides alcohols of retained configuration, some elimination and inversion products.



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BIS-CYCLOPENTADIENYL METAL COMPOUNDS

Reported by Edwin L. DeYoung

October 8, 1954

Ever since the discovery of ferrocene in 1951¹, interest has grown in the chemistry of bis-cyclopentadienyl metal compounds. Since the basic chemistry of ferrocene has been reviewed elsewhere^{2,4}, only a background sketch of it and its structure will be presented here. Neither of the two independent discoverers of ferrocene^{1,3}, elucidated the structure.

Woodward⁵ and coworkers first proposed the name "ferrocene" for bis-cyclopentadienyl iron (II), and pointed out the aromatic character of the two cyclopentadiene rings. They showed that the two rings showed none of the properties of polyolefinic systems, and that they would undergo Friedel-Crafts acylation. Upon oxidation of the acylated product, the resulting dicarboxylic acid had values similar to that of benzoic acid. $pK_1 = 3.1 \times 10^{-9}$, $pK_2 = 2.7 \times 10^{-8}$, while the pK for benzoic acid is 2.4×10^{-7} .

Wilkinson⁶ proposed the structure for a "molecular sandwich" in which the two cyclopentadiene rings are symmetrical with respect to the Fe atom.

(Fig. I) From the fact that IR spectra showed only one C-H absorption band at 3.25μ , all the C-H bonds in the cyclopentadiene rings are equal. The central Fe atom has the krypton structure, from 5π electrons from each ring, and 8 electrons from the Fe atom. Dunitz and Orgel⁷, verified this structure by X-ray diffraction studies. No evidence for free rotation of the rings could be found⁸.

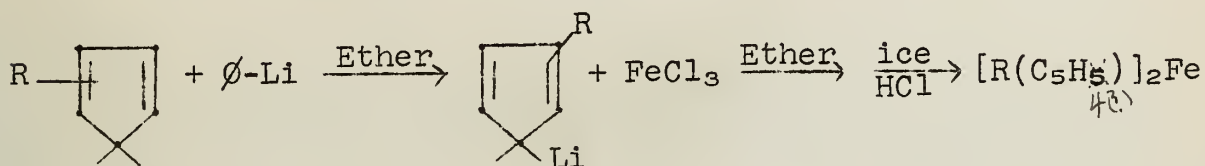


The question of the structure of ferrocene is still under discussion. Jaffe⁹ pointed out that the 18 valence electrons are distributed so that 16 of them occupy bonding and 2 non-bonding molecular orbitals. The stability of ferrocene was attributed to (a) rare gas configuration of the Fe atom. (b) existence of 8 bonding molecular orbitals, so that the Fe atom is bound to each of the rings by 4 covalent bonds. Fischer¹⁰ was the first to propose that the Fe atom was bound in octahedral coordination with the two fully aromatic cyclopentadiene rings. He also maintained that the electronic configuration is d^2sp^3 .¹¹

More recently, however, Wilkinson¹² has objected to the octahedral coordination theory because of the following deficiencies: (a) the phase symmetry conditions required by the octahedral theory are only approximated (b) evidence for the aromatic character of the cyclopentadienyl rings is not explained (c) the dative bonding required by octahedral coordination would result in negative charges on the central metal atom (This is not so.) (d) the known magnetic data are not explained (e) the presence of stable derivatives of transition elements of groups IV and V of the periodic table shows that the attainment of the structure of the next inert gas of the metal atom is of little importance.

Craig and co-workers¹³ have shown that the covalent π type bond is the most important and that the σ dative type bond increases in importance as the π bond is weakened by decrease in unpaired electrons. The most recent structural study of bis-cyclopentadienyl metal compounds by Moffitt¹⁴ has extended the hybridized molecular orbital theory to cover all the known metal compounds so far prepared.

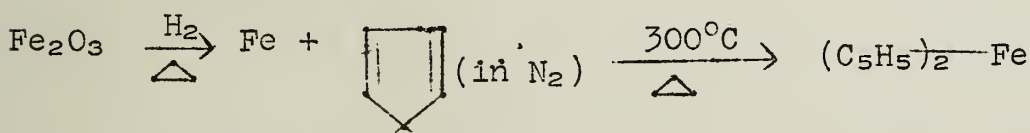
The most recent reports on the chemistry of ferrocene itself have been made by Pauson¹⁵ who has prepared a number of phenyl substituted ferrocenes. He used the following series of reactions:



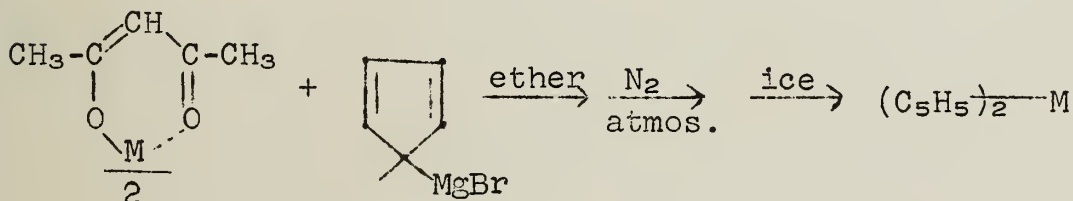
The total number of different metals which have been reported as bis-cyclopentadienyl derivatives now is 15.

There are six methods of preparation of bis-cyclopentadienyl metal compounds:

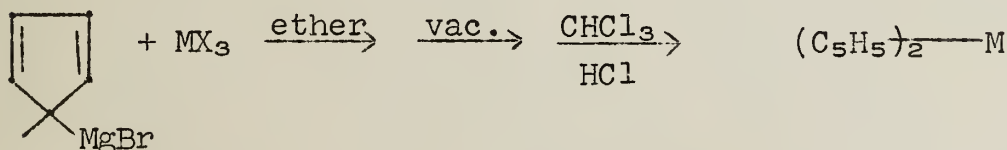
A. Passing cyclopentadiene vapors with N_2 over Fe at 300°C .³



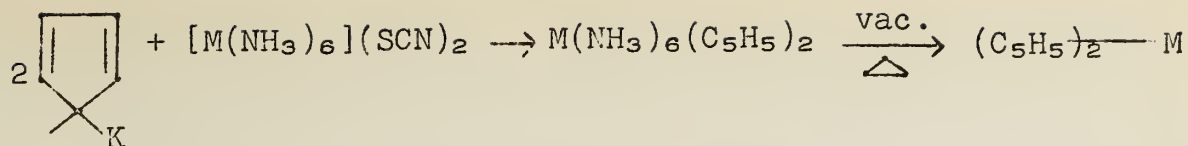
B. Treating a metal acetylacetonate with a cyclopentadienyl Grignard reagent. This has been used to prepare the following metal compounds: Ni (II), Fe (II),^{16,20}; Ru (III),¹⁷; Co (II), Co (III),¹⁸; Rh (III), Ir (III)¹⁹



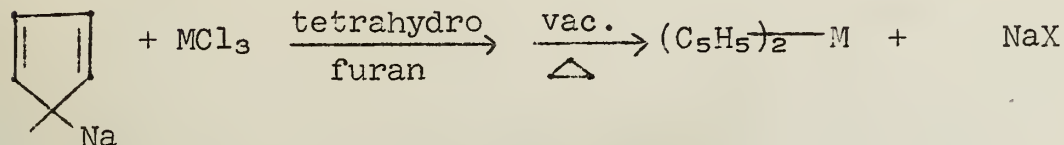
C. Treating the cyclopentadienyl Grignard reagent with an ethereal solution of the metal halide. This has been used for: Ti (IV), Zr (IV), V (IV),^{20,23}; Co (II),²¹; Fe (II),¹; Mg (II),²²; Nb (V), and Ta (V),²³.



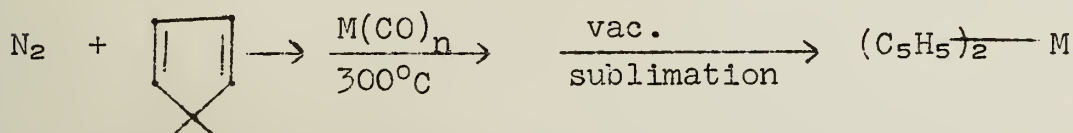
D. Treating cyclopentadienyl -K(or Na or Li) in liquid ammonia with a metal thiocyanate amino complex, and decomposing the salt by heating in vacuum. This has been used in the preparation of: Cr (II),²⁴; Ni (II),²⁵; and Co (II)²⁶.



E. Treating cyclopentadienyl -Na in tetrahydrofuran with the metal halide. This has been used for: Cr (II), Mo (IV), W (V),²⁹.



F. Treating a mixture of cyclopentadiene vapors and N₂ with metal carbonyls at 280-340°C. This has been used for: Cr (III), Mo (I), W (I),²⁷; Fe (II), Co (II), and Ni (II)¹⁶.



The majority of cyclopentadienyl metal compounds are neutral solids. However some of them: Ir (III), Rh (III), Co (I), Fe (I), Ru (I), Ti (III), V (III), Mg (I), and Ni (III), exist only in solutions and could not be separated as stable solids. Three of them are reducible polarographically: Rh (III) → Rh (II); Co (II) → Co (I); and Fe (III) → Fe (II)²⁸. Only four of them have been oxidized; Ru (II) → Ru (III), Fe (II) → Fe (III), Co (II) → Co (III), and Ni (II) → Ni (III). All of the bis-cyclopentadienyl metal complexes now known show strong diamagnetic or paramagnetic properties.

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ION-PAIRS AS INTERMEDIATES IN SOLVOLYSIS REACTIONS

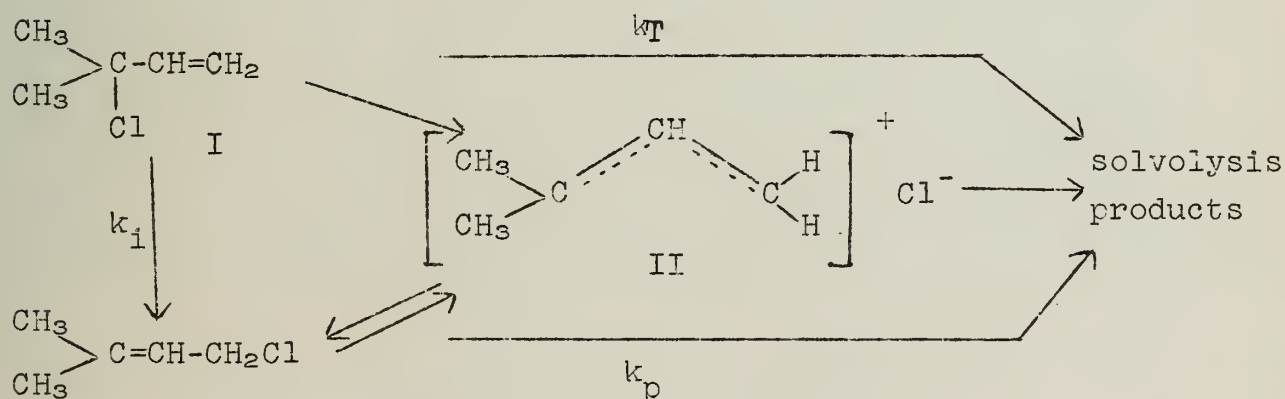
Reported by Arthur H. Goldkamp

October 15, 1954

In general, three forms of a weak electrolyte may be present in solution: (1) the undissociated species, AB, (2) the free ions, $A^+ + B^-$, and (3) ionic aggregates. The simplest case of (3) is that of an ion-pair, A^+B^- , which is held together by purely electrostatic forces.¹ The difference between (1) and (3) may be visualized by assuming that AB is essentially covalent and functions as an electrolyte only by virtue of the ionizing properties of the solvent. Thus, (3) might be expressed as sA^+B^- to indicate solvent participation (dispersion of charge) which induces heterolytic fission of the original covalent bond; (2), then, represents the completely solvated (free) ions.

Indications of ion-pairs derived from trityl (triphenylmethyl) chloride have been obtained by conductance measurements in liquid sulfur dioxide^{1,2} and by spectrophotometric analysis of solutions in various nitroalkanes.³ The first of these cases has previously been reviewed.⁴

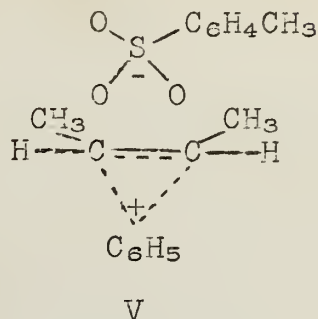
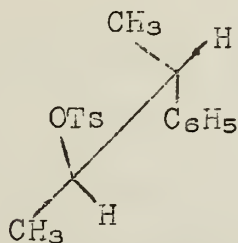
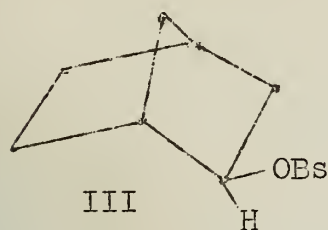
One of the first examples of a reaction found to be readily interpreted on the basis of a discrete ion-pair intermediate is the simultaneous rearrangement and acetolysis of α,α -dimethylallyl chloride (I).^{4,5} In this case a bimolecular (S_N2 or S_N2') mechanism can be eliminated on the basis of the constancy of solvolysis rate with various initial concentrations of potassium acetate. Thus, a unimolecular (S_N1) mechanism is involved in the solvolysis. The fact that the rate constant is independent of chloride ion concentration ("mass law" effect) strongly suggests the formulation of an ion-pair intermediate (II).



First order rate constants were measured for the irreversible reactions indicated: (a) acetolysis of the tertiary isomer, k_T , (b) acetolysis of the primary isomer, k_p , and (c) isomerization of the tertiary isomer, k_i . "Internal return"--collapse of the ion-pair to the primary isomer--would explain the lack of effect of chloride ion on the isomerization reaction. The other rate constants were also found to be independent of chloride ion concentration.

Further substantiation for the phenomenon of internal return has been obtained by polarimetric and titrimetric rate determinations in solvolysis reactions.^{6,7,8} Optically active

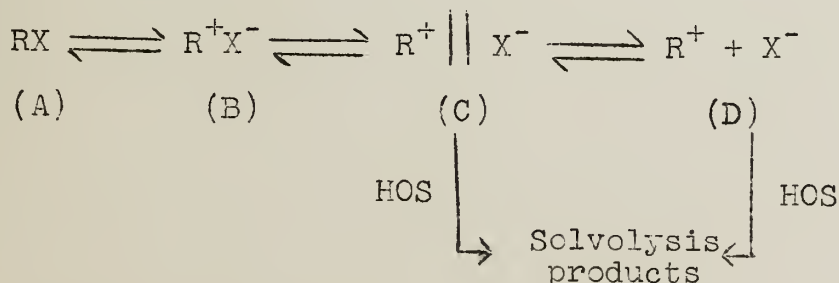
isomers of exo-norbornyl-p-bromo-benzenesulfonate (III)⁶ and 3-phenyl-2-butyl p-toluenesulfonate (IV)⁷ have been shown to solvolyze with first order rate constants which vary sharply with the ionizing power of the solvent.



Polarimetric rate constants for these and other examples generally exceeded those determined titrimetrically by factors of 1.5-5 depending upon the compound and solvent used. These and other details of the studies establish the necessary interpretation that ion-pairs, uninfluenced by external return ("mass law" effect), are intermediates in the solvolysis reactions. This is also supported by investigation of the products obtained from IV and the corresponding diastereomers in solvolysis reactions.⁹ For example, the intermediate in the solvolysis of IV is the phenonium tosylate ion-pair (V).

Ion-pairs also appear to be intermediates in the rearrangement of various 9-decalylperesters^{10,11,12} since the reaction, though shown to be ionic,¹³ does not give any indication of significant exchange with ions of similar structure.

Recently, Winstein and co-workers have published evidence from salt effects for a second, "solvent separated", ion-pair which may constitute another intermediate in solvolysis reactions.^{14,15} Their data for various systems such as those previously described show only small increases in polarimetric rate constants on addition of lithium perchlorate, whereas the titrimetric values rise rapidly at first with increasing salt concentration and then slowly as they approach the polarimetric values. Thus, added salt eliminates a substantial part of ion-pair return and, in the following scheme, would exert its effect at the solvent separated stage (C).



The data, moreover, demand the further interpretation that the two types of ion-pairs differ essentially in that (C) exchanges with solvent, whereas (B) does not.

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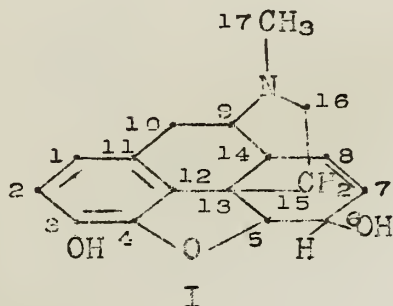
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SYNTHESIS OF MORPHINE

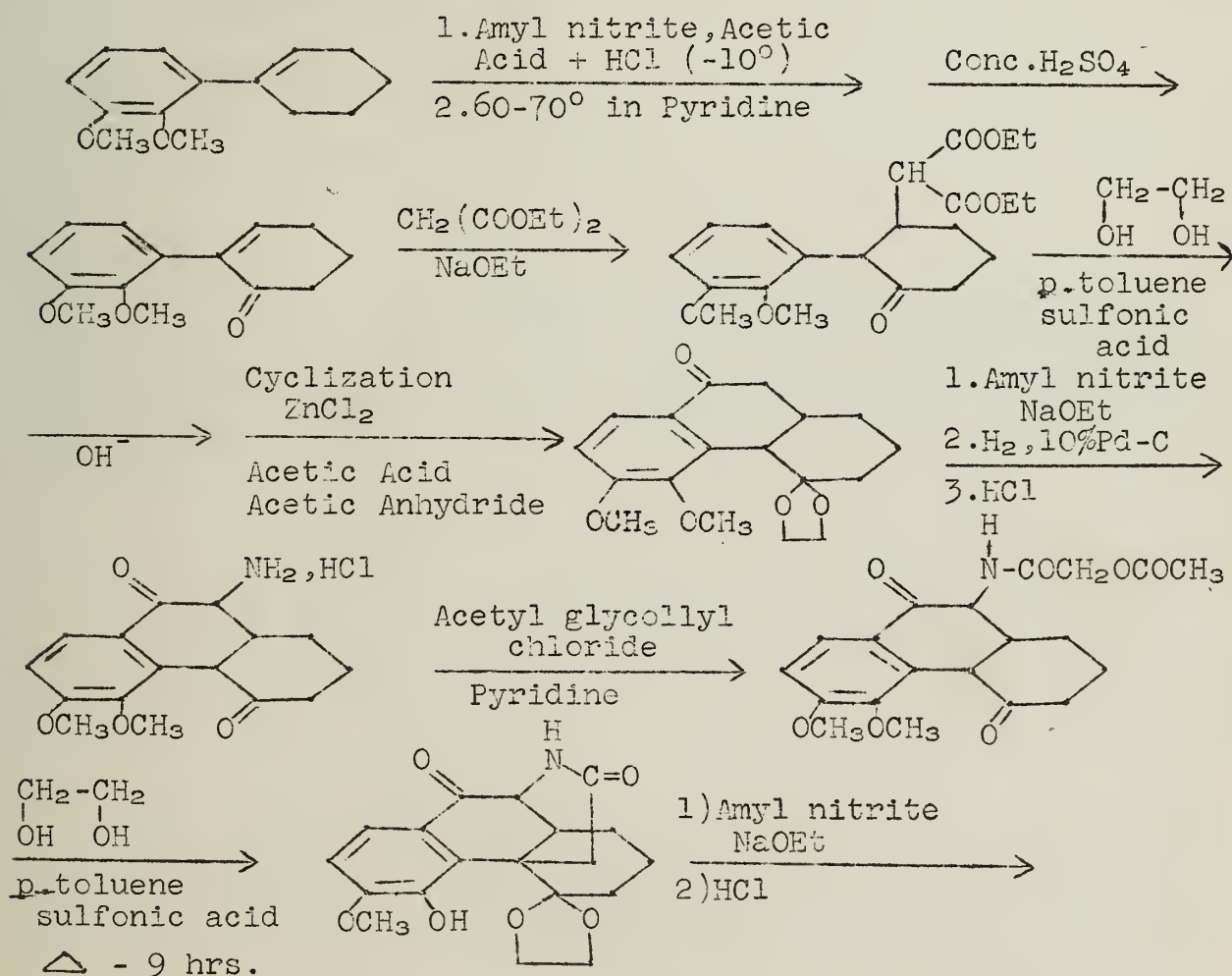
Reported by Mohan D. Nair

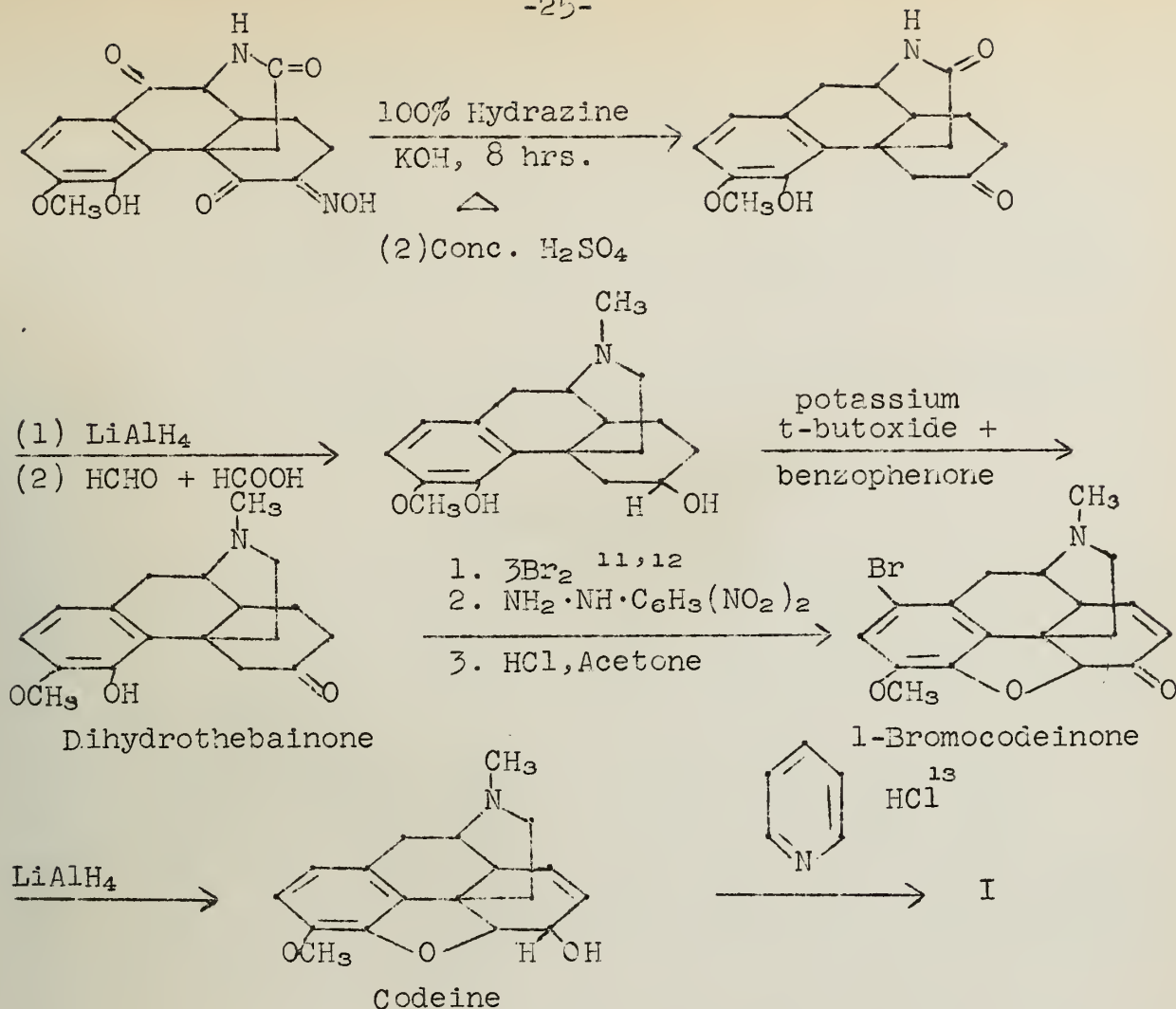
October 15, 1954

The problem of the structure of morphine has attracted attention in the past seventy years. Even though Structure I was proposed as early as 1923¹, direct experimental proof has been available only since 1952 when the first total synthesis was reported^{2,3,4,11}. A new synthesis of this alkaloid has been completed this year by Ginsburg and Elad^{5,6,7,8,9,10}.

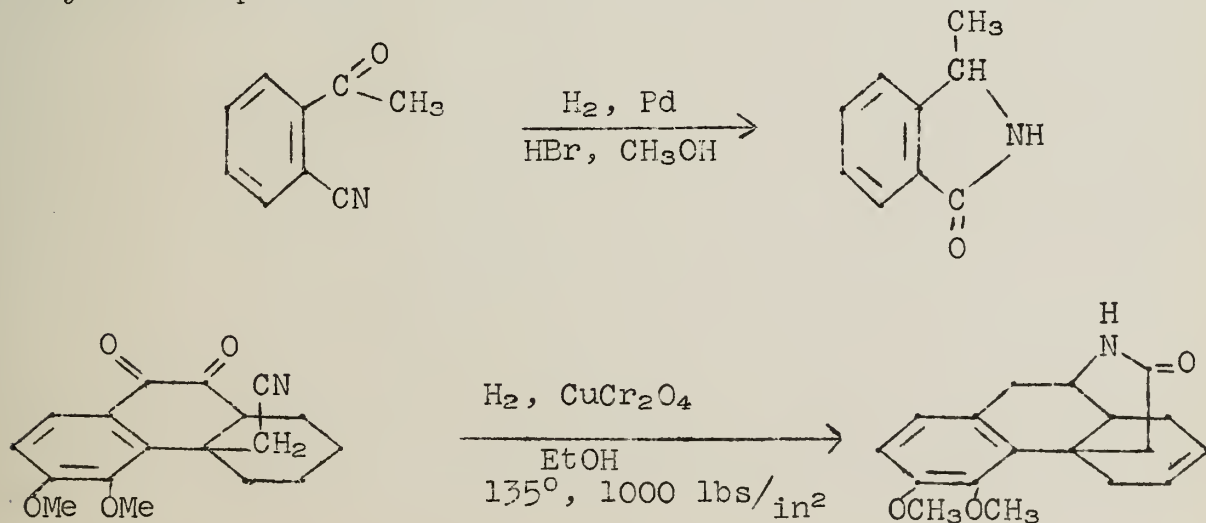


This new synthesis has been accomplished in the following manner:





Most of the early attempts to synthesise morphine failed mainly because of the difficulty of putting the nitrogen bridge ring between C_9 and C_{13} . Gates and Tschudi in their synthesis carried out the closing of the lactam ring by hydrogenation over cu -chromite catalyst; a reaction analogous to the reduction of o -cyanoacetophenone.



It is very interesting that this reaction was accomplished in the new synthesis quite unexpectedly and with considerable ease. Furthermore, demethylation of the C_4 methoxy group also occurred

during this cyclization.

Introduction of the double bond between C₇ and C₈ in dihydrothebainone was effected by treatment with Br₂ and 2,4-dinitrophenyl hydrazine in acetic followed by hydrolysis with HCl. The closing of the oxide ring occurs by a displacement reaction of the phenolate anion on C₅ which carries a bromine after bromination using 3 moles of the halogen.

The demethylation reaction by which codeine is converted into morphine was carried out as early as 1951 by several workers using pyridine hydrochloride.

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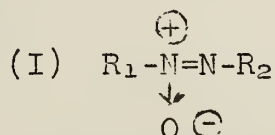
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STRUCTURAL AND GEOMETRICAL ISOMERISM IN THE OXIDATION OF AZO COMPOUNDS

Reported by D. F. Morrow

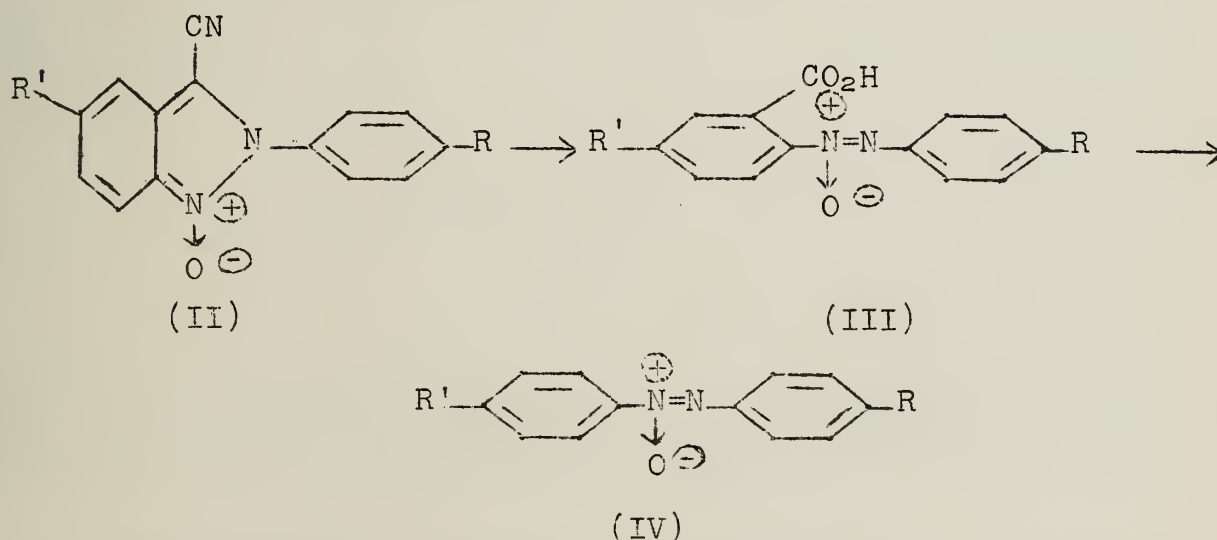
October 22, 1954

Azoxy compounds (I) are formed upon oxidation of aromatic azo compounds. That azoxy compounds have such a structure was first postulated by Angeli¹ and was later proven by Marvel².



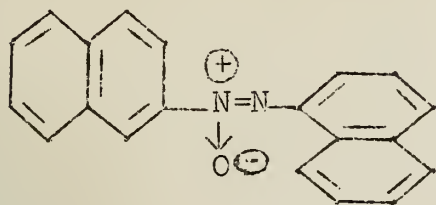
Two structural isomers may be formed when $R_1 \neq R_2$, and studies of these isomers in the phenyl series have been carried out by Angeli *et al*³ and by Behr⁴. Angeli's approach to the problem was mainly concerned with investigating the bromination and nitration of azoxy compounds prepared from azobenzene (where $R_1=R_2$), and comparing the unsymmetrical product obtained in each case with the two isomers which are formed in the oxidation of *p*-bromoazobenzene and *p*-nitroazobenzene. The structures for the two *p*-bromo- and *p*-nitroazoxybenzenes which were assigned by Angeli were based upon the ease of formation of one of the isomers from azoxybenzene itself. He postulated that the ring removed from the $\oplus N \rightarrow O \ominus$ group was more readily attacked by electrophilic reagents.

This year Behr established that these structures were correct by unequivocal syntheses of the various isomers. Vigorous oxidation of substituted indazole oxides (II) followed by the decarboxylation of the acid formed (III) led to azoxybenzenes (IV) in which the relationship of the substituted ring to the nitrogen atom bonded to oxygen was definitely known.

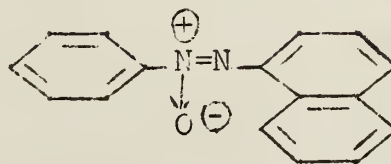


Badger *et al*^{5,6,7} have recently isolated and studied the products formed by the per-acid oxidation of unsymmetrical azo compounds. In the azonaphthalene and phenylazonaphthalene series, kinetic data and ultraviolet spectra indicate that the nitrogen atom next to a 1-position in naphthalene is oxidized only with difficulty, and that it is not oxidized at all if an alternative oxidation is possible. Thus, the perbenzoic acid oxidation of 1,2'-azonaphthalene and 1-phenylazonaphthalene give V and VI

respectively. Steric hindrance by the 8-position, as well as the superior conjugating ability of the 1-position of naphthalene were advanced as explanations for this.



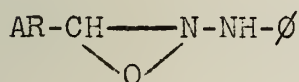
V



VI

Geometrical isomerism about the N to N double bond in azo compounds has been demonstrated⁸. Although the cis and trans forms of azoxy compounds have been known for some time, the probability of isolating the cis form of an azo compound was considered extremely unlikely.⁹ However, modern consensus of opinion is that the cis and trans forms do exist separately and that they have been isolated.⁸ The per-acid oxidation of the cis and trans forms of azobenzene leads to cis and trans azoxybenzenes, respectively. The much faster rate of oxidation of the cis isomer shows that the double bond and the free electron pairs of the nitrogen atoms are only slightly conjugated with the phenyl groups. Reduction of both cis and trans azoxybenzenes with lithium aluminum hydride, however, leads only to the more stable trans azobenzene.¹⁰

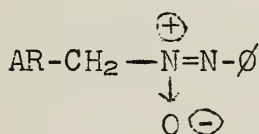
Primary aliphatic azo compounds have lately been oxidized to the corresponding azoxy compounds.¹¹ Along the same line, the product of the per-acid oxidation of phenylhydrazones, previously thought to have the structure of either VII or VIII, is now considered to have structure IX.^{12,13}



VII



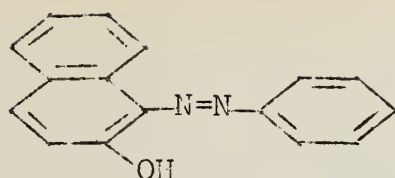
VIII



IX

Infrared spectra show the presence of an azoxy grouping, and the fact that the bromination product of IX is identical with the oxidation product of the p-bromophenylhydrazone indicates that the oxygen atom is bonded as shown.^{12,14}

Recent investigations of the light-catalyzed rearrangement of azoxy compounds into hydroxy-azo compounds has led to some interesting results. The hydroxyl group formed is always ortho to the azo linkage and on the ring removed from the nitrogen atom to which the oxygen atom was originally bonded. Thus VI, upon a month's standing in sunlight, gave X in 5-15% yield.¹⁵



X

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STEREOCHEMICAL ASPECTS OF THERMOCHROMISM

Reported by John W. Johnson, Jr.

October 22, 1954

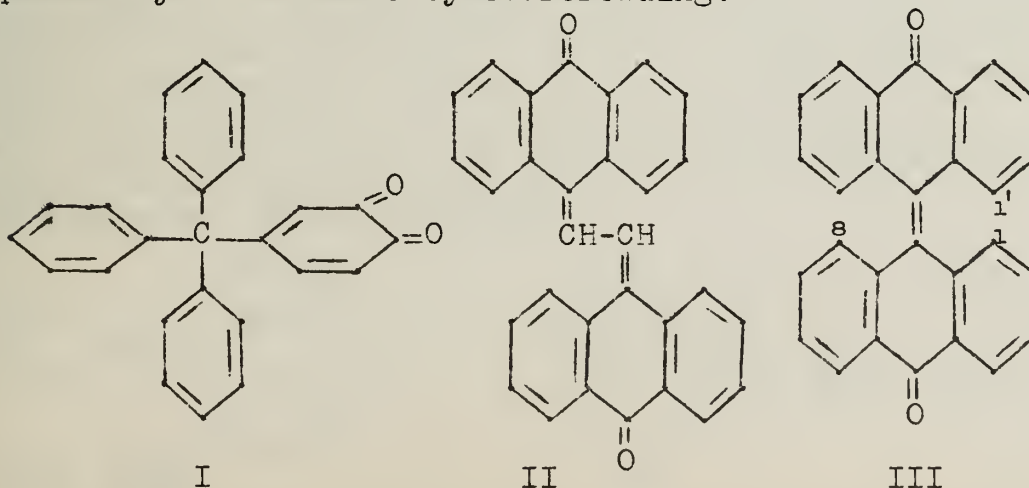
The change of color with temperature or thermochromism of numerous organic compounds, has been of interest for many years. Thermochromism, as used in this seminar, will imply "reversible" changes in the color of solutions, observable with the naked eye, occurring between 0°C. and higher temperatures.

Several mechanisms which have been advanced to explain this property are:

- (1) reversible thermal dissociation into free radicals¹,
- (2) thermal equilibrium between the true ethylene structure (classical sense) and the betaine structure in which the population of the heteropolar species increases with rise in temperature^{2,3,4,5},
- (3) broadening of a near ultraviolet absorption region, caused by changing the distribution of molecules among vibrational states at elevated temperatures^{6,7,8},
- (4) existence of distinct electronic levels situated 3-5 kilocalories above the ground state of the colorless modification, attainable as a result of the energy absorbed at elevated temperatures^{6,9,10}.

Chemical evidence has resulted in completely discarding the first mechanism^{11,12}, while experimental results tend to support in part the other three mechanisms. In general, it is agreed that thermochromism is due to a change in planarity of the molecule, the colored modification having a greater degree of planarity^{13,14,15,16,17}. That planarity is of importance in any theory of thermochromism is indicated by the nature of the substances which have been reported to have this property. They are usually "overcrowded" molecules possessing in many cases conjugated chromophores and conjugated auxochromes. In many cases these compounds are colorless at room temperature¹⁸.

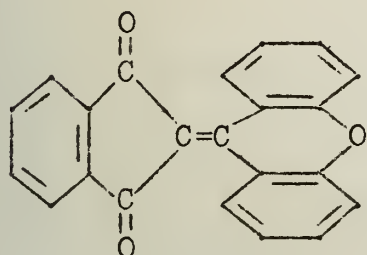
Thus while the comparatively planar molecules benzil, phenanthraquinone and acenaphthenequinone are non-thermochromic, 4-(triphenylmethyl)-1,2-benzoquinone (I), which is pronouncedly non-planar, is thermochromic. 1,2-bis-(9,9-Anthronylidene)-ethane (II), a compound related to the thermochromic bianthrone (III), was found to be thermochromic also. In both compounds planarity is hindered by overcrowding.



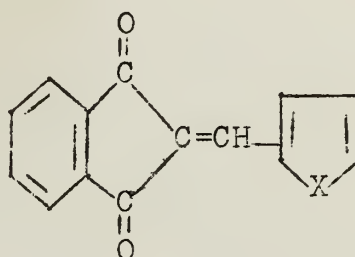
This theory quite naturally leads to predictions of the effect of changes in structure on thermochromic substances:

A. Overcrowding of the molecule to such a degree that planarity is hindered even at high temperatures, should destroy the thermochromic properties of certain molecules. This effect has been shown most conclusively in the spiropyrans¹². Also when III is substituted at positions 1' and 1 or 8, the resulting molecule shows no thermochromic properties^{9,18}.

B. A decrease in overcrowding would permit certain molecules to approach planarity at room temperature which should cause a loss of thermochromic properties. Thus, whereas 2-(9-xanthylidene)-indan-1,3-dione (IV) is thermochromic, its analogs, 2-(2-furfurylidene)-indan-1,3-dione (Va) and 2-(2-thienylidene)-indan-1,3-dione (Vb) show no thermochromism.

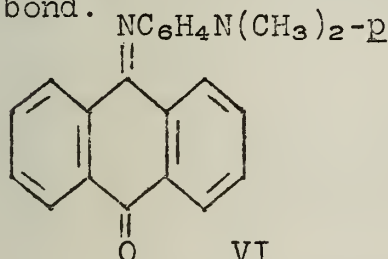


IV

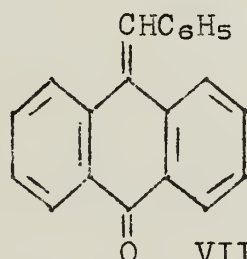


Va, X=O; Vb, X=S

An interesting case is anthraquinone-mono-p-dimethylamino-anil (VI), which is thermochromic, while 9-benzylideneanthrone (VII) is not. This difference may be explained by the fact that VII is less crowded since the C=C bond is longer than the C=N bond.

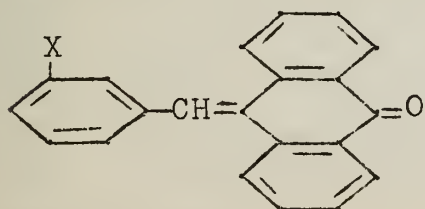


VI

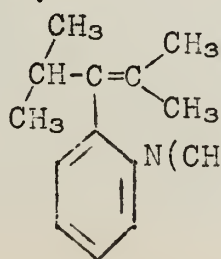


VII

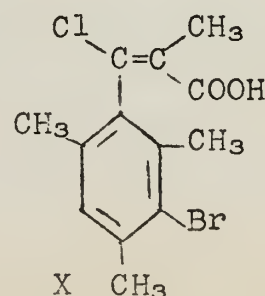
10-(m-Nitrobenzylidene)-anthrone (VIIIa) exhibits pronounced thermochromism. Its reduction product VIIIb does not¹⁹. VIIIb was also expected to show restricted rotation about the single bond between the phenyl group and its side chain by analogy with the resolvable compounds IX²⁰ and X²¹. VIIIb could not be resolved by crystallization of its (+)-10-camphorsulfonate. Optical activity was inferred by the mutarotation of this salt and by the preparation of its active hydroiodide salt. It is well known that the ease of resolution of compounds containing a single pivot bond with restricted rotation is related to the non-planarity of the molecule²².



VIIIa, X=NO₂
VIIIb, X=NH₂



IX



X

Hirshberg and Fischer^{23,24} have shown that low-temperature irradiation, with light of wavelengths less than 4500 Å, of solutions of thermochromic compounds produces reversible color changes (photochromism) analogous to the high-temperature color changes. Comparison of the absorption spectra of the thermochromic and photochromic colored modifications has shown that they are probably identical. Moreover, compounds which differ from known thermochromic substances by having a greater degree of overcrowding, exhibit photochromism but not thermochromism. Thus, it is plausible that the reason for the non-thermochromic properties of these compounds is due to the fact that the temperatures employed were not sufficiently high to establish the necessary planar configuration.

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A NEW METHOD FOR THE PREPARATION OF OLEFINS--THE PYROLYSIS OF SULFITES

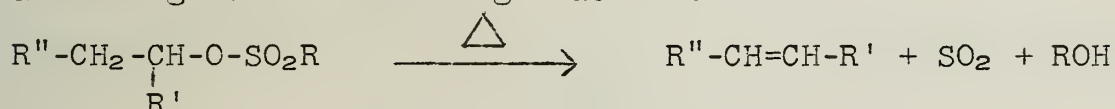
Reported by F. M. Scheidt

October 29, 1954

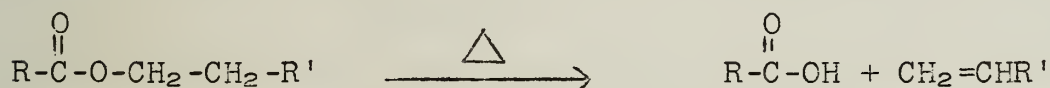
Two of the most widely used methods for preparing olefins are catalytic or chemical dehydration of alcohols and pyrolysis of xanthates or other esters. The catalytic or chemical dehydration of alcohols is sometimes disadvantageous because elimination of water may take place with alteration in the carbon skeleton.¹

The pyrolysis of xanthates, the Chugaev method of preparing olefins, is useful because olefins can be prepared in this manner from sensitive alcohols without rearrangement of the carbon skeleton thus avoiding a mixture of rearranged products.^{2,3}

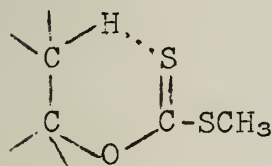
A third pyrolytic method of olefin preparation has been reported recently by Berti⁴, who, with Price⁵ in previous work on the pyrolysis of symmetrical organic sulfites found that a principal decomposition product was always an olefin formed according to the following reaction:



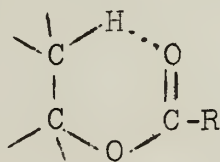
It would appear that the mechanism of the pyrolysis of these sulfites might have a close similarity to the other pyrolytic elimination reactions, that is, to the Chugaev reaction and the thermal decomposition of esters such as:



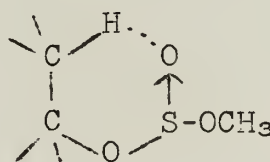
Both of the latter two reactions are usually thought to take place by a concerted mechanism involving cyclic transition states represented by (I)^{6,7,8} and (II)⁹, respectively. It would seem that a similar transition state (III) could be written also for the pyrolysis of methyl alkyl sulfites.⁴



(I)



(II)



(III)

A number of sulfites were prepared and pyrolyzed: methyl α -methylphenethyl sulfite (IV), methyl 3-phenylpropyl sulfite (V), methyl cis-2-phenylcyclohexyl sulfite (VI) (plus the trans-isomer), L-menthyl methyl sulfite (VII), and methyl cholesteryl sulfite (VIII). The pyrolysis yields are listed below:

<u>Compound</u>	<u>Decomposition Temperature (°C)</u>	<u>Total Olefin Yield (%)</u>	<u>Olefins Produced</u> *
IV	245	92	allyl benzene (45%) propenyl benzene (55%)
V	260	45	allyl benzene (100%)
<u>cis</u> -VI	200	93	3-phenylcyclohexene (22%) 1-phenylcyclohexene (78%)
<u>trans</u> -VI	200	88	3-phenylcyclohexene (35%) 1-phenylcyclohexene (65%)
VII	215	35	2-menthene (35%) 3-menthene (65%)
VIII	185	53	3,5-cholestadiene (100%)

* Percentages given indicate percent of total olefin yield.

The olefins produced by the pyrolysis of IV indicate that the course of the reaction is independent of the influence of conjugation of the phenyl ring. However, pyrolysis of VI gave results differing from those Alexander¹⁰ observed in pyrolysis of both the xanthate and corresponding acetate:

<u>Compound</u>	<u>Total Olefin Yield (%)</u>	<u>Olefins Produced</u> *
methyl <u>cis</u> -2-phenylcyclohexyl xanthate (<u>cis</u> -IX)	71	3-phenylcyclohexene (96%) 1-phenylcyclohexene (4%)
methyl <u>trans</u> -2-phenylcyclohexyl xanthate (<u>trans</u> -IX)	---	3-phenylcyclohexene (12%) 1-phenylcyclohexene (88%)

* Percentages given indicate percent of total olefin yield.

Alexander reports almost the same proportions of olefins from the pyrolysis of the corresponding acetates.

The differences between the pyrolytic products of cis- and trans-VI and those of cis- and trans-IX would suggest that the assumption of similar cyclic transition states for the pyrolysis of xanthates and organic sulfites is questionable, although, of course, other unknown factors may explain these differences. Although O'Connor and Nace^{9,11} report that a study of the Chugaev reaction shows that a cis-configuration of the eliminated groups is required, a different mechanism must sometimes be assumed. For example, the pyrolysis of a xanthate with no cis- β -hydrogen, methyl cis-2-methyl-1-indanyl xanthate, yields a small amount of 2-methyl indene.¹²

Price and Berti⁵ noted quite a difference in the stabilities to pyrolysis of some symmetrical alkyl sulfites:

<u>Compound</u>	<u>Decomposition Temperature (°C)</u>
α -carbethoxybenzyl sulfite (X)	250
α -methylbenzyl sulfite (XI)	110

If ionization were involved in the reaction, it would be hindered in the pyrolysis of X and favored in the case of XI. Further supporting evidence has been given by Lewis and Boozer¹³ who found that ion-pairs are involved in the decomposition of secondary alkyl chlorosulfites. Price⁴ proposes a mechanism involving ion-pairs in the decomposition of organic sulfites.

Before the scope and limitations of the pyrolysis of methyl alkyl sulfites as a method for the preparation of olefins can be stated, further investigation of the reaction will have to be made. However, based on the work already completed by Berti and Price,^{4,5} it can be said that yields were higher than in the corresponding Chugaev reaction; preparation of the methyl alkyl sulfite was less time-consuming than preparation of the xanthate, and the olefin produced was quite pure, containing only small amounts of dimethyl sulfite. An undesirable feature of the pyrolysis of methyl alkyl sulfites is its apparent lack of stereospecificity.

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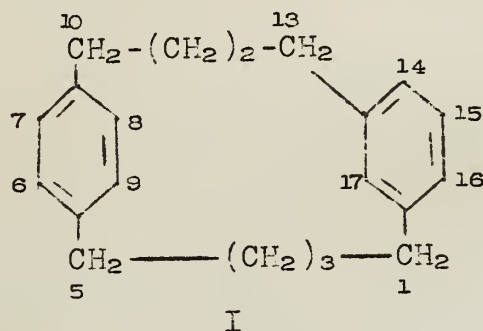
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RECENT STUDIES OF MACROCYCLIC RING SYSTEMS: CYCLOPHANES

Reported by Fred P. Hauck, Jr.

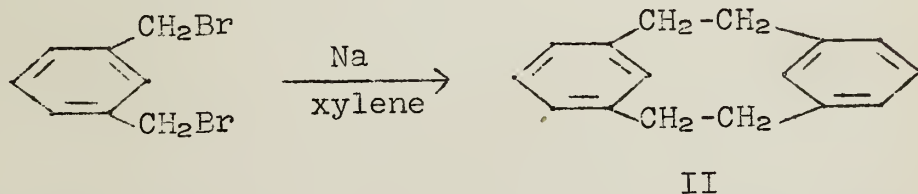
October 29, 1954

Cyclophanes include those macrocyclic compounds in which one or more benzene rings are joined o, m or p by aliphatic chains. A numbering system has been proposed (I).¹ This is a 5-p-4-m-cyclophane, where the numbers in the name indicate the number of carbon atoms in the bridges.

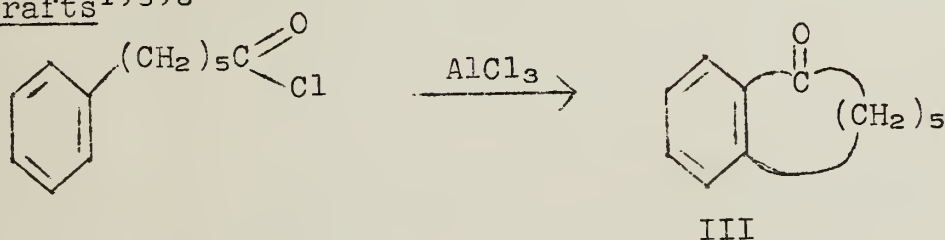


SYNTHESES - A number of useful syntheses have been developed for various types of cyclophanes.

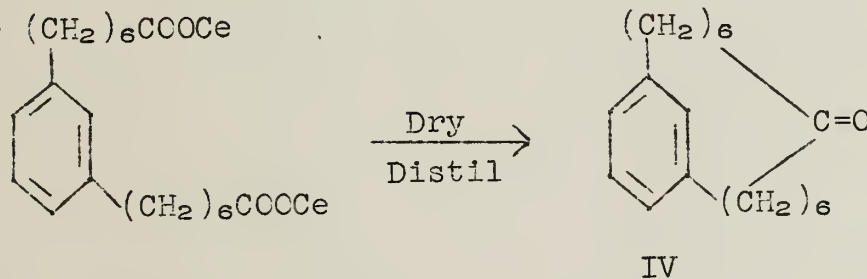
Wurtz²⁻⁴



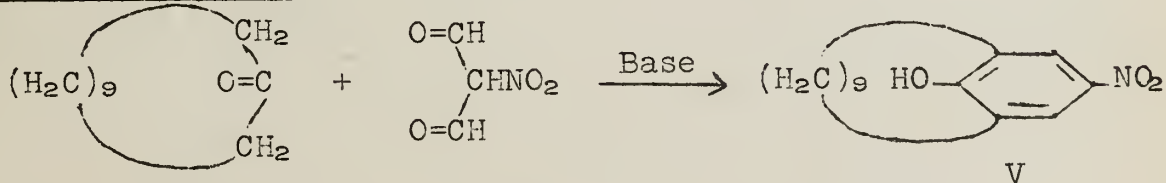
Friedel-Crafts^{1,5,6}



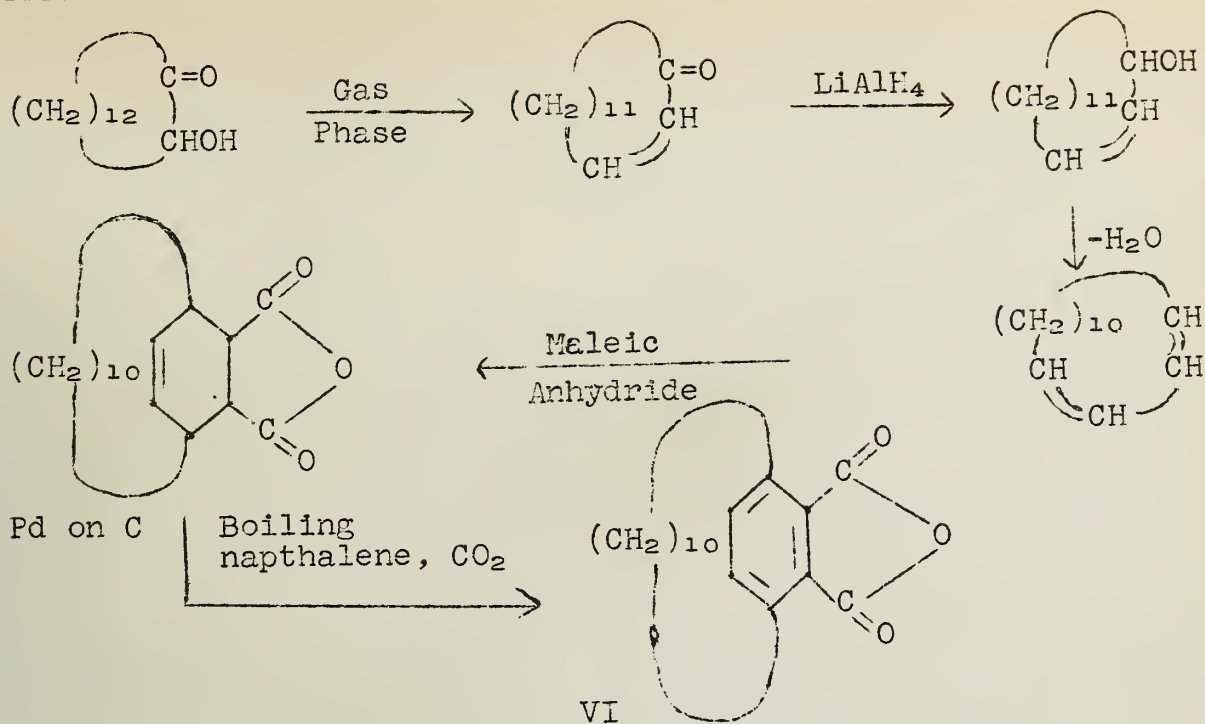
Pyrolysis⁷ (CH₂)₆COOCe



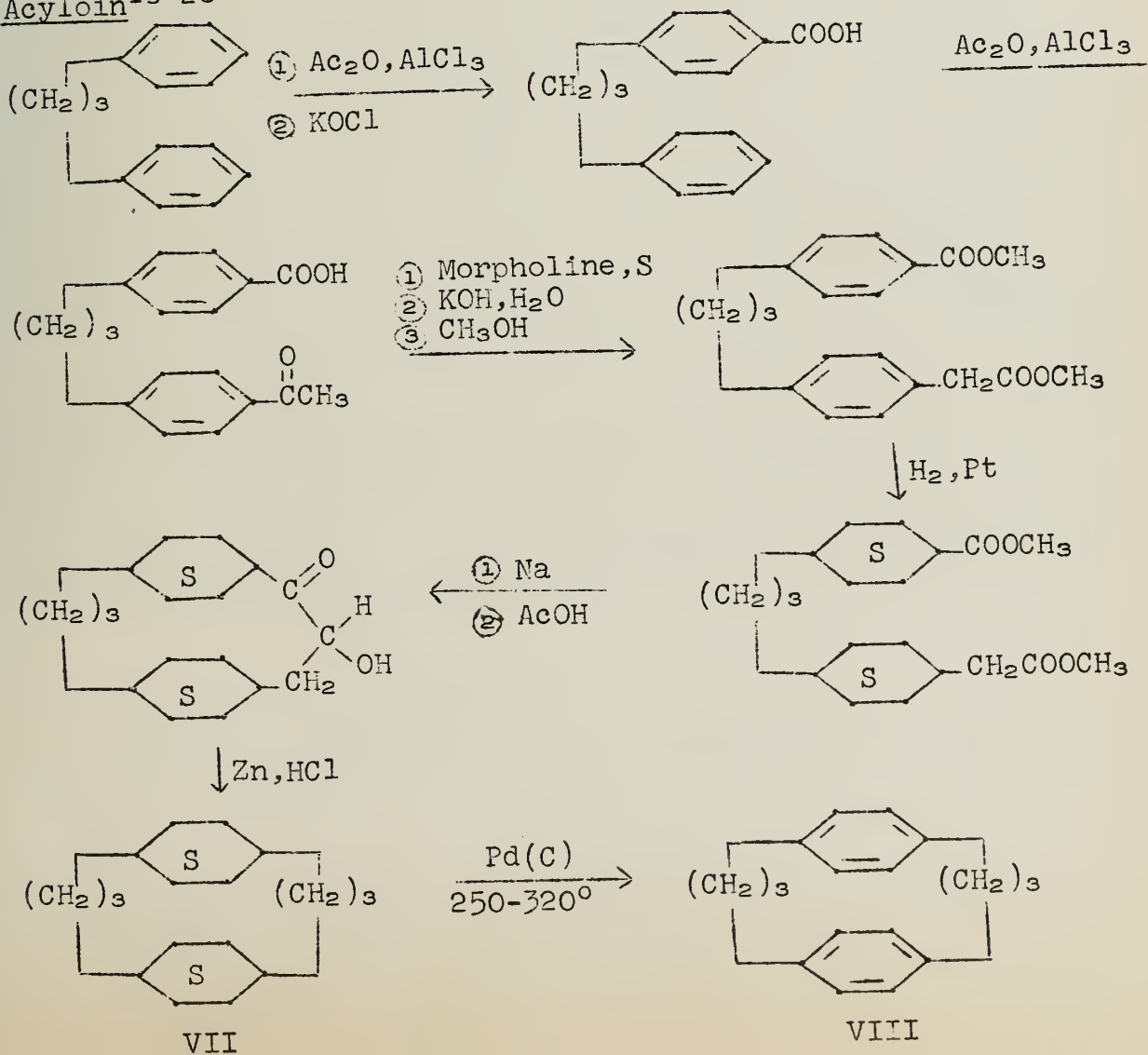
Nitromalonaldehyde⁸⁻¹¹



Diels-Alder^{12,13,14}

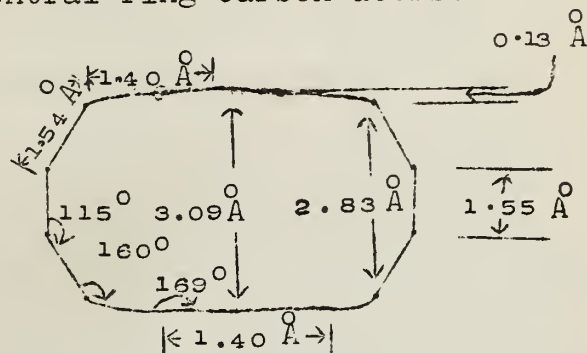


Acyloin¹⁵⁻²³



STRUCTURE - Detailed crystal structures for di-p-xylylene (II)^{24,25} and di-m-xylylene²⁶ show that the benzene rings are not planar and that the bond angles are distorted. The m-bridged compound is centrosymmetric and the two halves form a stepped system in which the benzene rings are boat-shaped to achieve adequate separation between the central ring carbon atoms.

Thus, in compounds of this type, the aromatic properties of the rings are affected by ① the non-planarity of the benzene rings and ② the overlap of π -orbitals.^{17,23} For the paracyclophanes (e.g., VIII), the series from two 2-membered bridges to a 4- and a 6-membered bridge have been prepared¹⁹⁻²³ and the extent of these



II (Cross-section)

two factors have been studied by means of u.v. spectra. A shift toward longer wavelengths and lower intensities was observed as the aliphatic bridges became smaller. In systems where the two bridges contain 4 or more carbon atoms each, the benzene rings are planar, and no spectral alterations were noted. In the smaller systems the interplanar distances have been calculated to be less than the normal 3.40 Å noted in many substances (graphite, coronene, etc.). Similar spectral shifts have been noted in the monobenzene cyclophanes^{1,27} and these suggest that the 3-carbon aliphatic bridge places a strain on the monobenzene system comparable to that in the paracyclophane with two 3-carbon bridges. Other studies in the monobenzene systems^{5,6} have shown that in compounds of type III, large rings tend to force the carbonyl group out of coplanarity with the ring and thus cause a lowered reactivity toward additive reagents and a shift in spectrum toward that of an aliphatic ketone. Work in the bridged p-nitrophenol series⁸⁻¹¹ again reveals a shift toward higher wavelengths as the bridge decreases in size below nine carbons, as well as a shift toward lower reduction potentials (stabilization of oxidized form) and an increased acidity.

STEREOCHEMISTRY - Two types of stereoisomerism are to be expected with compounds of the cyclophane type^{20,23}: ① that due to relative configuration of points of attachment of bridges to cyclohexane rings (see VII) and ② that due to restricted rotation of the benzene ring(s). The latter type would be expected in the systems 4-p-4-p- or 4-p-5-p- but not in 5-p-5-p-cyclophane, in which rotation is not restricted.

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MECHANISM OF THE PARA-CLAISEN REARRANGEMENT

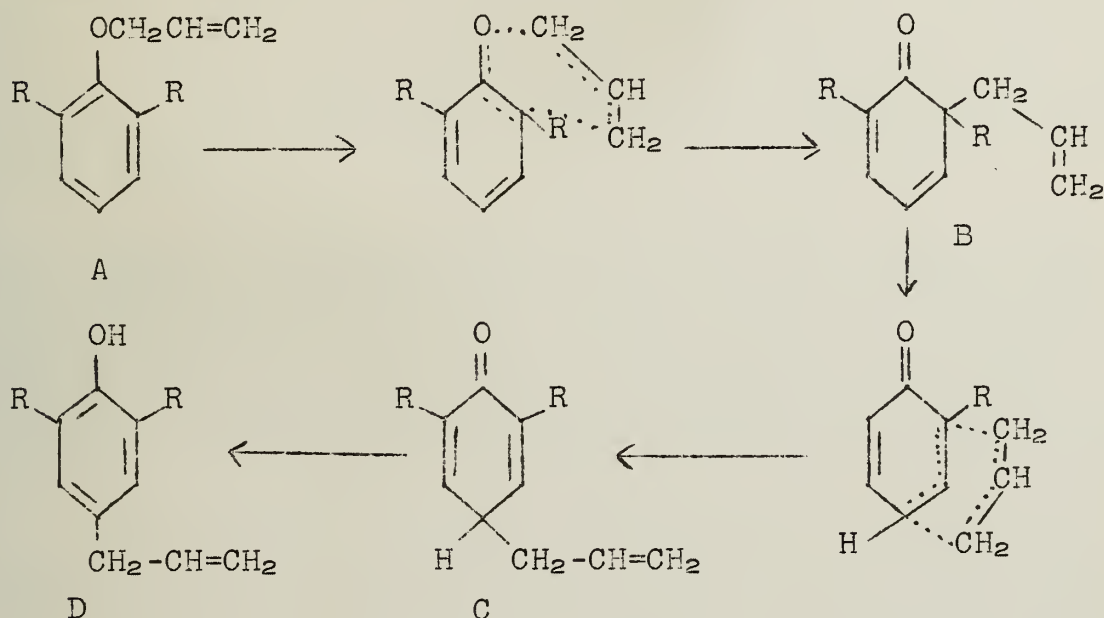
Reported by Hugh H. Gibbs

November 5, 1954

The para-Claisen rearrangement, first discovered by Claisen and Eisleb¹ in 1913, involves the rearrangement of the allyl ethers of 2,6-disubstituted phenols to the para-allyl derivatives. This seminar discusses the two main mechanisms proposed and their validity in view of some recent work.

Bicyclic Mechanism

The following mechanism has been proposed by Hurd and Pollack³:



The reaction appears to be intramolecular because of the non-alkylation of solvents such as dimethylaniline². Non-inversion of the allylic group (i.e. the α -carbon of the allylic group in the ether becomes the α -carbon in the para-position of the phenol) is well established. The radio-carbon work of Ryan and O'Connor⁴ and Schmidt and Schmidt⁵ on unsubstituted allyl groups as well as other studies on α -substituted⁶ and γ -substituted allyl groups^{7,8,9} all indicate non-inversion. An original report by Mumm and co-workers^{7,9} that inversion did occur with an α -substituted allyl group was shown by Rhoades, Raulins and Reynolds^{10,11} to be incorrect. The concept of non-inversion and the intramolecularity of the reaction is also supported by the work of Alexander and Kluiber¹² who found that optically active allyl ethers retained some activity after rearrangement.

The presence of the dienone, B, has been demonstrated by Conroy and Firestone¹³ who detected it by the isolation of a Diels-Alder adduct when the reaction was carried out in the presence of maleic anhydride at 200°. Pyrolysis of the adduct gave the para-Claisen product. Control experiments showed that the phenol gave no trace of adduct on heating with maleic anhydride and hence was not in equilibrium with the dienone. Also, believing that the high temperature used

to form the adduct might lead to a spurious reaction, the ether was first heated alone at 200° for 10 minutes, cooled to 100°, and the maleic anhydride added. Some adduct was still obtained.

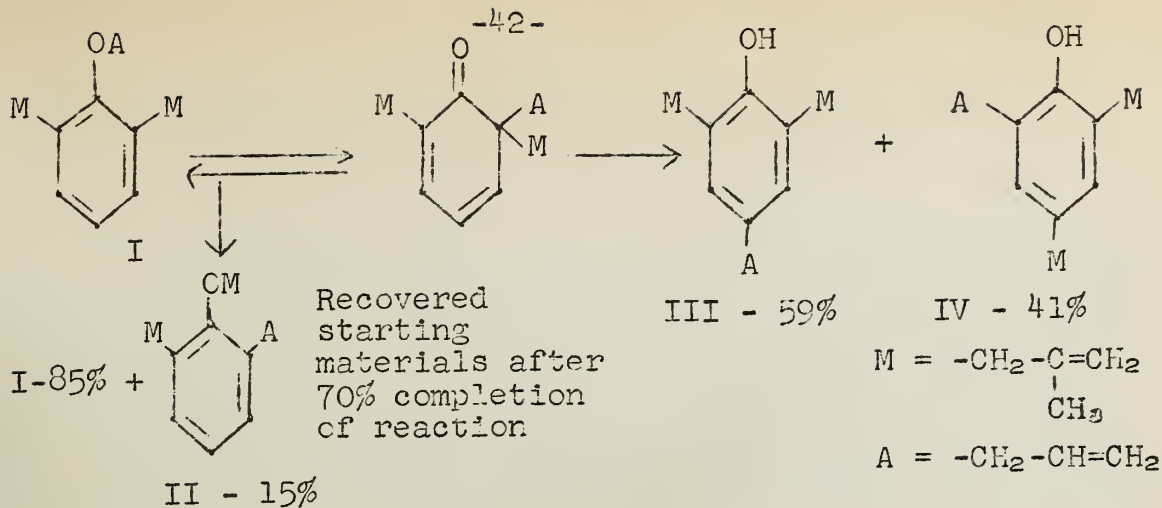
Further support for the presence of a dienone comes from Schmidt, Haegeler and Schmidt¹⁶. 1-Allyloxy-2-allyl-6-allyl- α -C¹⁴-benzene upon rearrangement gave a product in which 30% of the original C¹⁴ was to be found in the para-position.

Pi-Complex Mechanism

As an alternative to the bicyclic mechanism Dewar¹⁴ proposed that there could be interaction of the allyl group with the pi-electron cloud of the benzene ring with migration of the allyl group from the oxygen atom down the ring to the para-position. Since this would lead to inversion Ryan and O'Connor⁴ have modified the mechanism by suggesting that the allyl carbonium ion might be unsymmetrically attached to the aryl anion.

Now, although a dienone has been shown to be present, the possibility remains that it is not in the direct path between ether and para-rearrangement product. Indeed, B might rearrange to D via A. If such were true and if the ortho substituents were allylic but different from the original O-allyl group, then, on reversion from dienone to ether a rearranged ether might be obtained which might then by the Dewar mechanism rearrange to the para-Claisen product.

This problem of whether the dienone lies directly between ether and product or whether it is just formed by a side reaction has recently been solved by Curtin and Johnson¹⁵. They found that 1-allyloxy-2,6-dimethallyl benzene, I, rearranged to give a mixture of 4-allyl-2,6-dimethallyl phenol, III (59%) and 2-allyl-4,6-dimethallyl phenol, IV (41%). However, after 70% of completion of reaction, analysis of the residual phenol ether starting material indicated 85% of I and only 15% of the rearranged ether, 1-methallyloxy-2-allyl-6-methallyl benzene, II. Since only a small amount of rearranged ether was found in the recovered starting material while the products indicated a large amount of the para-methallyl phenol, IV, the latter must have come from the dienone directly and not from the rearranged ether via a pi-complex mechanism.



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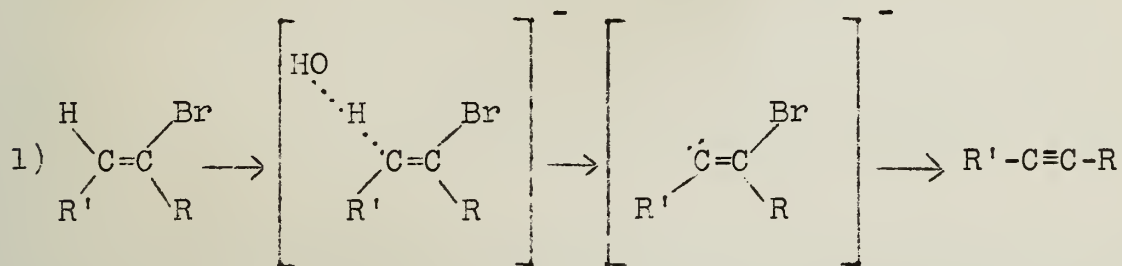
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A PROPOSED MECHANISM FOR BASIC cis-DEHYDROHALOGENATION

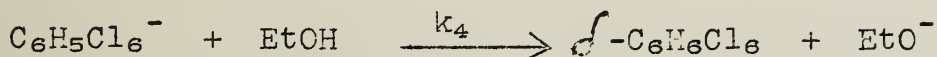
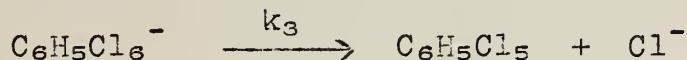
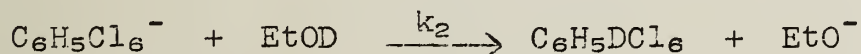
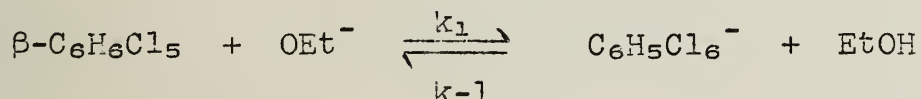
Reported by Robert M. Nowak

November 5, 1954

A stereochemical preference in second order elimination reactions has been shown in many cases¹⁻⁵; trans elements are removed more readily than cis elements. One of the suggested explanations for this preference is based upon a difference in mechanisms: trans groups are eliminated by a concerted one-stage mechanism; cis groups are eliminated by way of a carbanion intermediate and a multiple-stage process. Recent work by Cristol has given credence to his proposed mechanism for cis elimination which can be represented by equation (1).



Proof of a carbanion intermediate was accomplished by a deuterium exchange experiment⁶ on β -benzene hexachloride in which all neighboring hydrogen and chlorine atoms are cis. The significant equations involved in the reaction are⁷:



It is assumed that k_1 is the rate determining step of the elimination process. Since elimination is accompanied by a measurable deuterium exchange, k_2 must be roughly comparable to $k_3 + k_4$.

Deuterium exchange was realized to the extent of 0.083 ± 0.002 excess atom % which, calculations show, means that for every carbanion reverting to the deuterated β -benzene hexachloride, approximately 150 molecules disappear by other fates.

Knowledge of the mechanism of elimination was also obtained by comparing the energies of activation of the α, β, γ and ϵ isomers of benzene hexachloride in the elimination reaction. Only the β -isomer cannot undergo a trans-elimination of hydrogen chloride. On the basis of the proposed mechanisms for elimination it is assumed that cis-elimination will require a higher energy of activation than trans-elimination. Table I is in accord with this assumption.

Table I
Energies and Entropies of Activation⁸

Isomer	$E_{act.}$, (kcal/mole)	ΔS , (cal./deg.)
α	18.5	-1.0
β	31.0	20.2
γ	20.6	3.6
ϵ	21.4	6.5

It has been observed that the entropy of activation⁹ in cis elimination is larger than that for trans elimination, although exceptions to this rule are known.¹⁰ The entropy values of Table I⁸ follow this general rule, but in Table II⁹ trans-p-nitro- β -bromostyrene shows an opposite entropy effect. This anomaly can be rationalized in terms of steric hindrance of solvation on the reacting molecules and transition state ions.

If discrete cis and trans mechanisms of elimination exist, appropriate substitution of electron-attracting groups in the para-position of the isomers of β -bromostyrene should show a greater effect on the rate of cis elimination which requires a carbanion intermediate.

Table II^{9,11}

Rate Constants for Dehydrobromination with Sodium Hydroxide
in Isopropyl Alcohol

β -Bromostyrene	k	ΔS
<u>cis</u> -p-nitro	3.71×10^0	-4.0
<u>trans</u> -p-nitro	2.36×10^{-4}	-10.0
<u>cis</u>	3.00×10^{-3}	-5.6
<u>trans</u>	1.4×10^{-8}	+4.0

Table II shows that the electron withdrawing group has the greater effect on the rate of the trans isomer (cis elimination).

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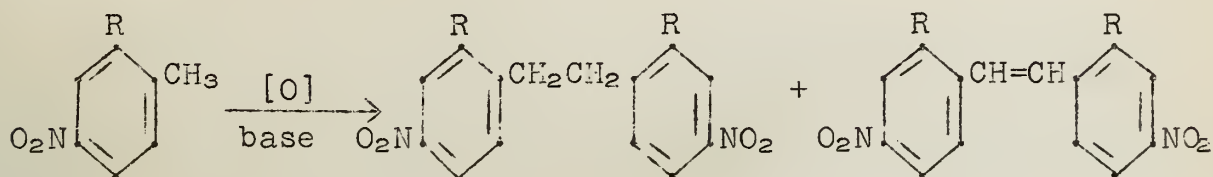
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THE SYNTHESIS OF SYMMETRICAL BIBENZYL AND STILBENE COMPOUNDS FROM NITROTOLUENES

Reported by F. W. Wassmundt

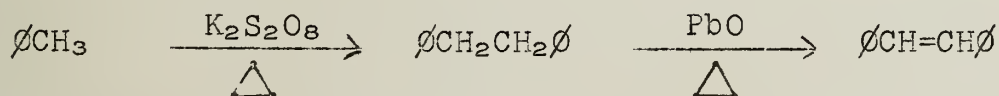
November 12, 1954

The self-condensation of nitrotoluenes in basic media was first observed by Fischer and Hepp ($R=H$, SO_3Na).¹ This



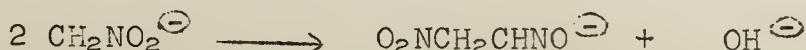
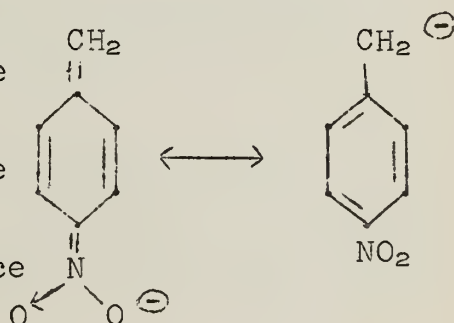
reaction was employed by Fischer and by Green^{2,3,4} for the preparation and investigation of possible dye intermediates. Subsequently, this condensation has been observed in attempted syntheses of other compounds: reactions involving basic reagents which effect nucleophilic substitution in aromatic nitro compounds^{5,6} or which attack active phenylmethylene compounds^{7,8} fail to give the desired product if attempted with *o*- and *p*-nitrotoluenes. Feissert's synthesis of ω -(*o*-nitrophenyl)-pyruvic acid⁹ from *o*-nitrotoluene, ethyl oxalate, and sodium ethoxide fails if the amount of base is doubled;¹⁰ the bibenzyl compound is formed instead.

Early attempts to explain the reaction compared it to the oxidation of Wolffenstein^{11,12} and of Behr and van Dierp.¹³



Certainly the first of these is a free radical reaction.¹⁴ This analogy was soon rejected when Wolffenstein showed that *p*-nitrotoluene does not condense when heated with potassium persulfate.¹⁵

The first systematic study was conducted by Plisov.¹⁶ The salient features of his mechanism proposal were the postulation of an intermediate quinoid structure and the reduction of one nitro group of the product to a nitroso group. Possibly the formation of the quinoid structure is important, for compounds which cannot form such a system do not react.^{16,17} This explanation has since been modified by Oda and Tsuruta¹⁸ who postulate that the oxidation removes an electron from the anion to produce a free radical. A recent study¹⁹ of the reaction of nitromethane (of which *o*- and *p*-nitrotoluenes are vinyls) tends to confirm some of Plisov's conjectures, as oxidation is unnecessary for the formation of the methazonate ion.



To date no mechanism has been proposed which explains the

reaction completely.

Conditions for Reaction

Base.--If the base is omitted, there is no reaction. The bases commonly used are potassium hydroxide or sodium ethoxide, though with 2,4-dinitrotoluene, ammonia or sodium carbonate are sufficient for condensation.⁴

Solvent.--Any solvent in which the starting material is soluble may serve. Generally, methyl alcohol has been employed. In one instance,²⁰ the condensation has been found to be more rapid in acetone than in alcohol. If an appropriate "solubilizing substituent" ($R=COONa$, SO_3Na) is present, water may serve as the solvent.

Oxidizing agent.--The choice of an oxidizing agent is dependent upon the solvent employed. In aqueous reaction mixtures, sodium hypochlorite acts as both base and oxidizing agent. The use of two equivalents of this oxidant favors the production of stilbenes. In alcoholic media, air is the preferred agent. Iodine can be used to advantage in non-aqueous solvents to produce stilbenes.^{4,21} It has been shown that in the absence of other oxidizing agents, the nitro compound itself serves as the oxidant.¹⁸

Nitro compound.--*m*-Nitrotoluenes do not react. Any substituted *o*- and *p*-nitrotoluenes except the hydroxy and acetoxy derivatives²² will undergo the reaction. Presumably these groups prevent the formation of the desired intermediate quinoid structure. Analogously, other electron donating groups tend to retard the reaction, while electrophilic substituents facilitate the condensation and often lead to stilbene compounds. If $R=NH_2$, OCH_3 , CH_3 , the reaction is carried out at reflux temperature; if $R=Cl$, Br , CN , H , at room temperature; if $R=COOH$, SO_3H , NO_2 , at ice-bath temperatures--reflux temperatures produce the stilbene compounds. The α -halogenated nitrotoluenes readily lend themselves to the synthesis of stilbenes.¹⁶

p-Nitroethylbenzene and *p,p'*-dinitrodiphenylmethane¹⁸ also undergo the condensation as well as some nitromethylnaphthalenes^{10,23} and nitromethylquinolines.¹⁷

The dinitrobibenzyls may be reduced in good yield²⁴ to the corresponding diamines which serve as useful intermediates. The bibenzyl prepared from 2-methoxy-4-nitrotoluene gives the corresponding hydrobenzoin when brominated, treated with silver acetate, and hydrolyzed. The corresponding benzil is formed when the hydrobenzoin is oxidized with nitric acid.²⁵

In one instance, a stilbene prepared in the manner described has been cleaved by the action of potassium permanganate to the corresponding aromatic aldehyde in almost quantitative yield.²

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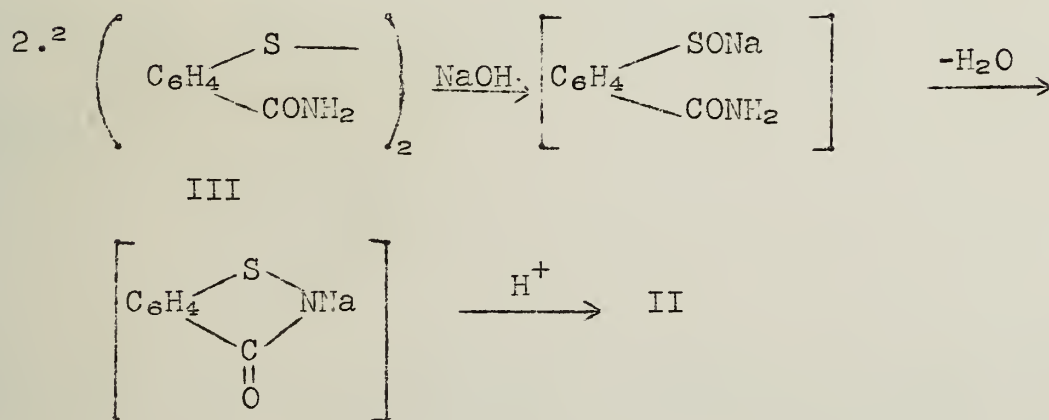
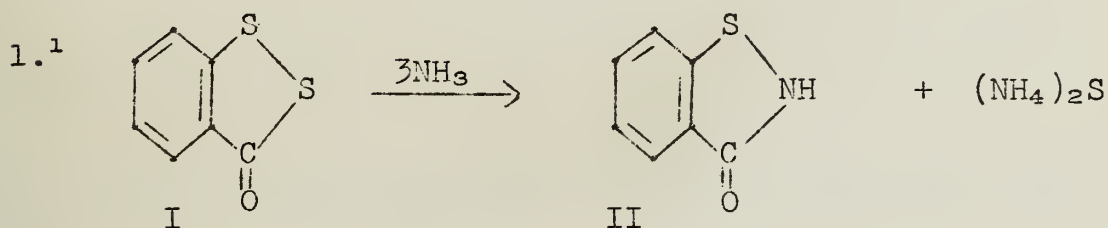
1,2-BENZISOTHAZOLONES

Reported by Frederick H. Owens

November 12, 1954

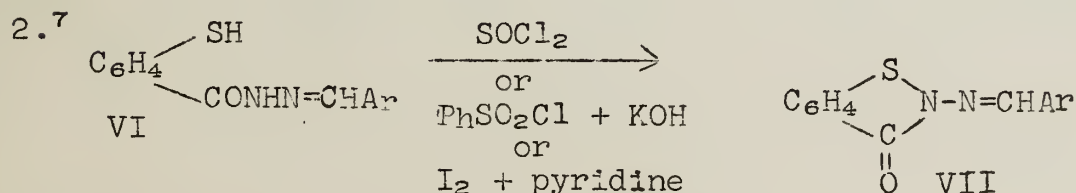
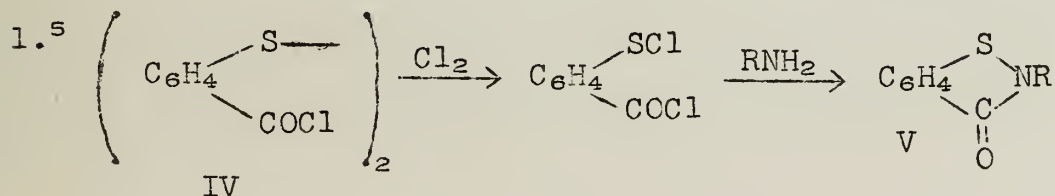
SYNTHESES

Three methods for the preparation of 1,2-benzisothiazolone (II) have been reported:



3. The reduction of o-cyanoarylsulfonyl chlorides with a reducing metal and a non-oxidizing acid.^{3,4}

Two general methods are applicable for the preparation of N-substituted-1,2-benzisothiazolones:

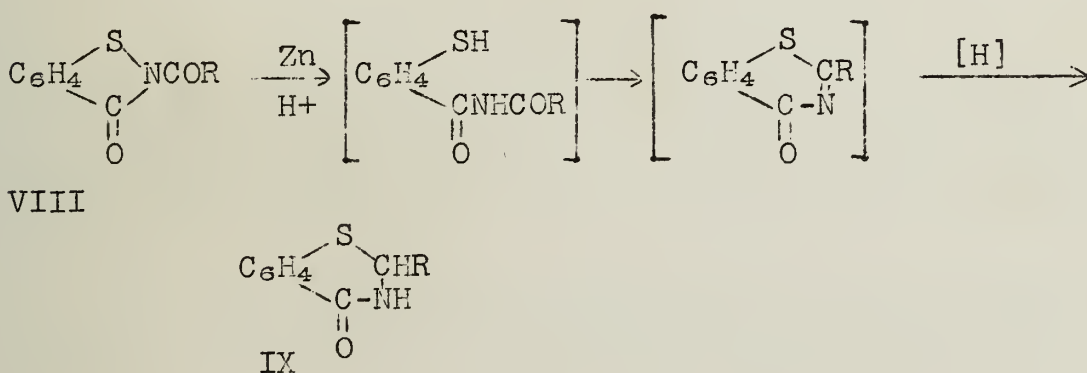
REACTIONS

1,2-Benzisothiazolone reacts with ferric chloride to give an intense purple color, showing that it enolizes

readily. Alkylation and reaction with arylsulfonyl chlorides produce both O and N substituted 1,2-benzisothiazolones; however, acylation and benzylation produce only N-substituted-1,2-benzisothiazolones. 1,2-Benzisothiazolone is acidic and forms metal salts readily.^{1,2,6,8}

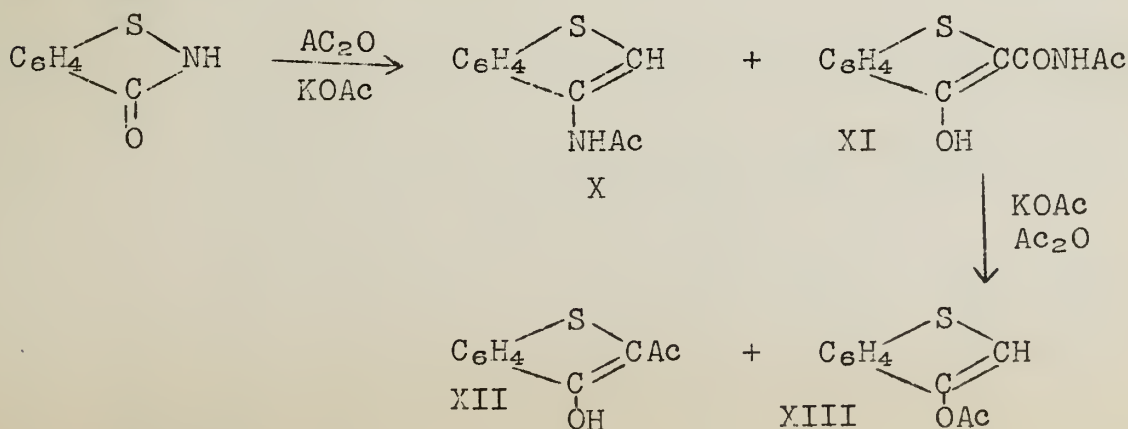
1,2-Benzisothiazolone is stable to acids and bases; however, N-alkyl or aryl substituted-1,2-benzisothiazolones, while they are stable to acids, are cleaved by strong bases.^{2,5} Acyl-1,2-benzisothiazolones are hydrolyzed by strong acids and bases to regenerate 1,2-benzisothiazolone. The N-arylsulfonates, on the other hand, are hydrolyzed by strong acid, whereas treatment with base causes hydrolytic ring cleavage.^{8,9}

N-acyl-1,2-benzisothiazolones (VIII, R=Me, Et, -CH₂Ph) are reduced by zinc and acid to 2-alkyl-(or aralkyl)-1,3-benzthiazine-4-ones (IX):¹⁰

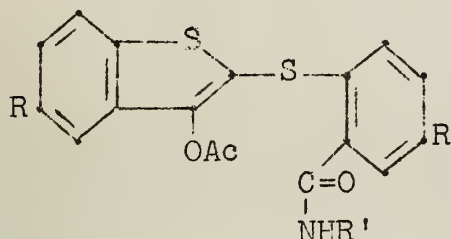


All other benzisothiazolones are reduced by zinc in acid, hydrogen iodide in acetic acid, or hydrogen sulfide to the correspondingly substituted 2,2'-dithiosalicylamides (III).^{1,2,5,8} 1,2-Benzisothiazolone is converted to benzonitrile by dry distillation with zinc.¹¹

When 1,2-benzisothiazolone is treated with acetic anhydride and potassium acetate at 50°, N-acetyl-1,2-benzisothiazolone is produced. However, when the temperature is raised above 70° and water is added to the reaction mixture, the products are 3-acetamido-1-thionaphthen (X), 3-hydroxy-2-acetylcarbonyl-1-thionaphthen (XI), 3-hydroxy-2-acetyl-1-thionaphthen (XII), and 3-acetoxy-1-thionaphthen (XIII). No definite mechanism for this reaction has been established.^{12,13,14,15}



With N-aryl or alkyl-1,2-benzisothiazolones, the radical attached to the nitrogen atom is not displaced; the products are XI (Ac replaced by R), XII, and XIII. With 5-chloro-1,2-benzisothiazolone or its N-acetyl derivative, the products are 5-chloro-X, 5-chloro-XII, 5-chloro-XIII, and a compound having the structure XIV, believed to have been formed by the reaction of 5-chloro-XI and 5-chloro-N-acetyl-1,2-benzisothiazolone.¹⁶



XIV: R=Cl, R'=Ac

XV: R=H, R'=SO₂Ar

XVI: R=Cl, R'=SO₂Ar

With N-acyl-1,2-benzisothiazolones other than N-acetyl-1,2-benzisothiazolone, the primary reaction is the replacement of the acyl group by the acetyl group with the subsequent reaction of the N-acetyl-1,2-benzisothiazolone in the manner previously described. However, a small amount of 3-acylamido-1-thionaphthen is produced, showing that not all of the original acyl group is replaced by the acetyl group.¹⁷

With N-arylsulfonyl-1,2-benzisothiazolones, the products are XII, XIII, N-acetylarylsulfonamides, and XV. With 5-chloro-N-arylsulfonyl-1,2-benzisothiazolones, analogous products are produced, with XVI predominating.¹⁶

Grignard reagents react with the carbonyl group of N-alkyl and aryl-1,2-benzisothiazolones to form the expected products, but with N-arylsulfonyl-1,2-benzisothiazolones, ring cleavage results.^{18,19}

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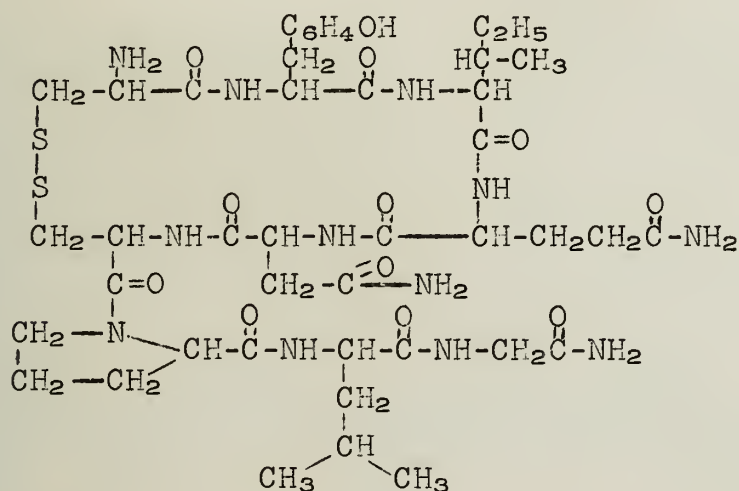
THE SYNTHESIS OF OXYTOCIN

Reported by Wendell W. Moyer, Jr.

November 19, 1954

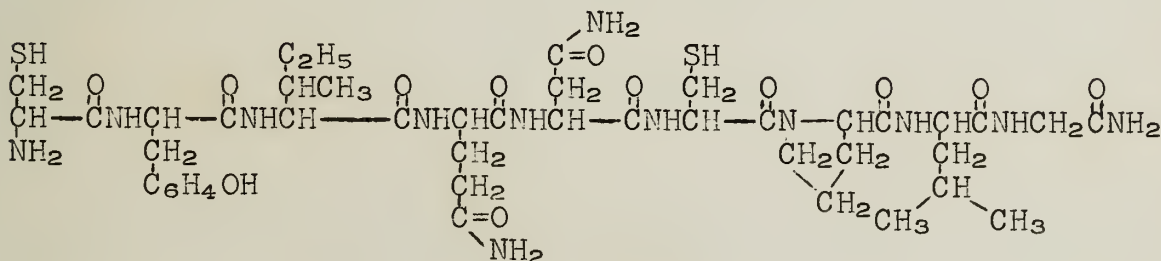
Studies have indicated that oxytocin, the principle uterine contracting and milk ejecting hormone of the posterior pituitary gland, has an approximate molecular weight of 1000 and on hydrolysis yields equimolecular amounts of leucine, isoleucine, tyrosine, proline, glutamic acid, aspartic acid, glycine, cystine, and three equivalents of ammonia.²⁻⁴

Evidence obtained through performic acid oxidation,⁵ desulfurization with Raney nickel,⁶ bromine water degradation,⁷ and determinations of terminal groups and amino acid sequence, by partial acid hydrolysis, led to the postulated structure of oxytocin.⁸⁻¹¹ (I)



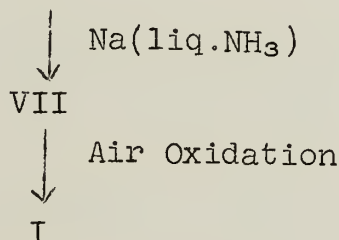
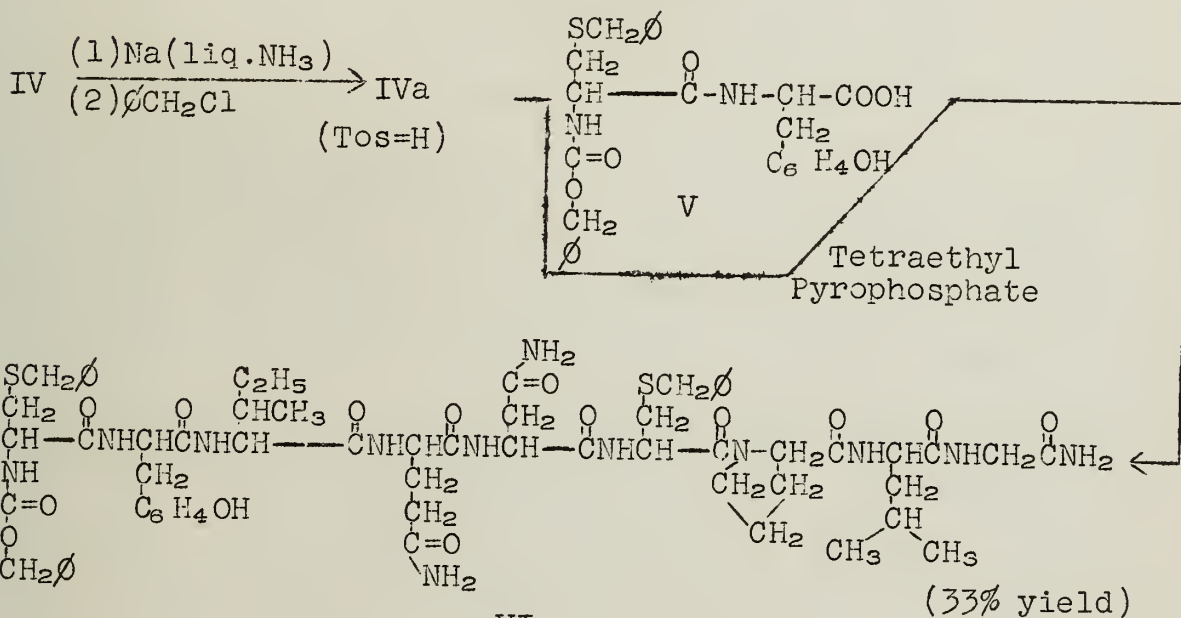
I

Since reduction of oxytocin yields but one product and the original material may be regenerated by aeration,^{12,13} compound VII should be easily converted into I.



VII

The synthesis of VII was accomplished by du Vigneaud and coworkers in the following manner:¹⁴⁻²⁰



The crude active material was purified by counter current distribution²³ in a system 0.05% acetic acid-sec-butyl alcohol. Analysis of the distribution indicated that the synthetic material had the same partition coefficient ($K=0.35$) as natural oxytocin. Potency of the synthetic material was carefully checked against that of the most highly purified natural oxytocin and found to check closely within experimental error. Amino acid analysis: Leucine 1.00, isoleucine 1.00, tyrosine 0.83, proline 0.92, glutamic acid 0.91, aspartic acid 0.93, glycine 0.98, cystine 0.87 and ammonia 3.04. No significant differences were detected in infrared patterns. The synthetic material

had $[\alpha]_D^{21.5} -26.1 \pm 1.0$; natural material $[\alpha]_D^{22} -26.2^\circ$. The synthetic product forms the same flavianate as the natural material, and exhibits the same electrophoretic mobility on paper. Other physical and chemical properties were identical within limits of experimental error.^{14,24} The synthetic material was also fully effective in stimulating uterine contraction in humans and possessed the expected milk ejecting activity.²⁵

This synthesis constitutes the first synthesis of a polypeptide hormone.

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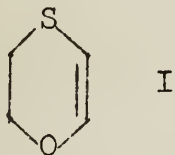
SYNTHESIS AND PROPERTIES OF DITHIADIENE AND SOME RELATED COMPOUNDS

Reported by Ralph Farrar

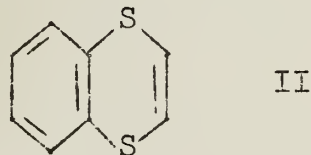
November 19, 1954

Recently a series of papers have appeared which are concerned with the synthesis and properties of the following compounds:

p-Oxathiene¹



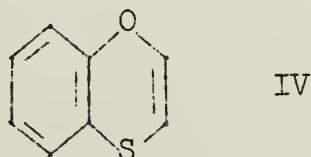
Benzo-1,4-dithiadiene^{2,4,5}



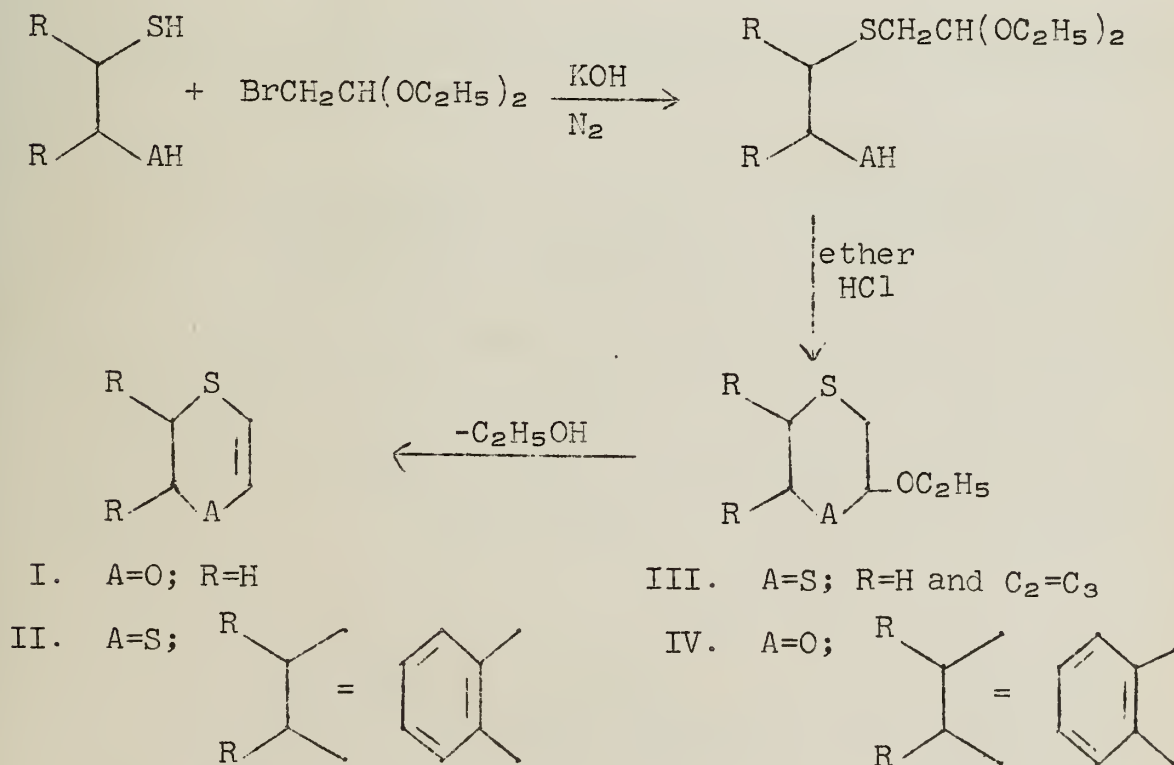
1,4-Dithiadiene^{3,5,6}



Benzo-1,4-oxathiadiene⁴



These compounds were prepared by the following scheme:

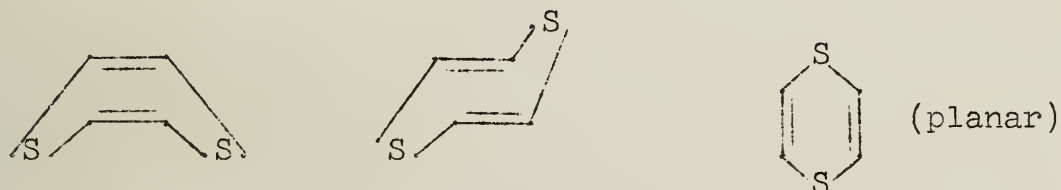


The purpose of the study of these compounds was two-fold: (1) to gain a better understanding of the electronic effects of sulfur and oxygen in ring systems of this type and (2) to establish the aromatic or aliphatic character of these compounds.

It has been stated by Baddeley⁷ and Schomaker and Pauling⁸ that oxygen releases electrons in the direction of its covalent bonds much easier than does sulfur. Parham also found evidence to support this conclusion in the mode of addition to the double bond of p-oxathiene.

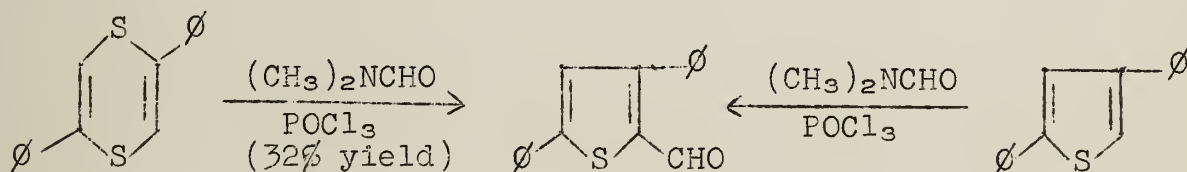
The dithiadene ring in benzo-1,4-dithiadene has been shown to undergo some of the reactions characteristic of an aromatic ring more readily than the heterocyclic ring of benzo-1,4-oxathiadene. This could be explained by assuming that the type of resonance responsible for the greater stability of thiophene with respect to furan is greatly increased by the presence of two sulfur atoms in benzo-1,4-dithiadene.

Since dithiadene could possibly exist in one of the following three forms:

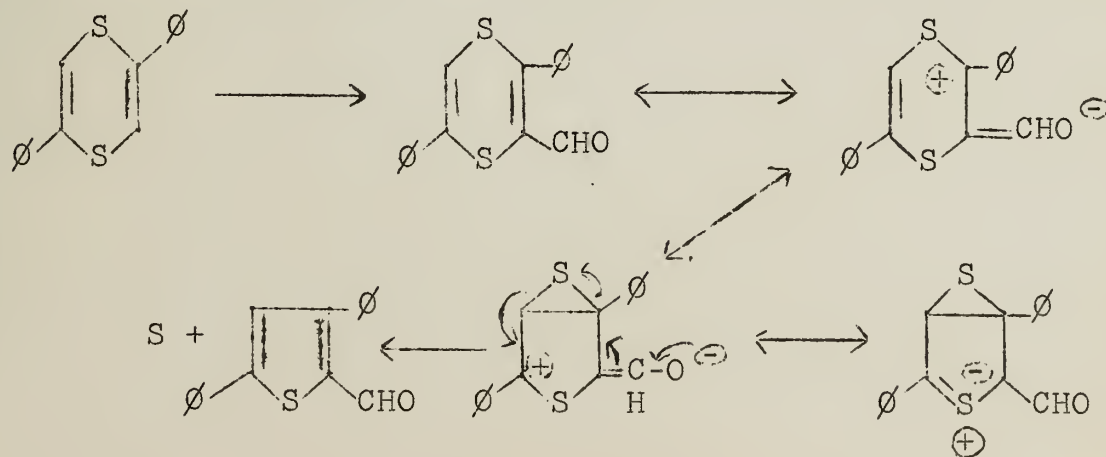


a single crystal study of the compound was carried out. The results of this work indicate that dithiadene exists in the first or "boat" form.⁵

A very interesting rearrangement of the dithiadene ring has been studied.⁶



The rearrangement has been postulated to occur as follows:



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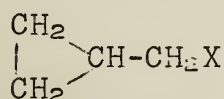
CARBONIUM ION REARRANGEMENTS IN THREE AND FOUR MEMBERED RINGS

Reported by J. W. Crump

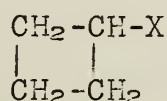
December 3, 1954

Introduction

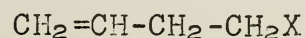
Treatment of either Ia or IIa with nitrous acid results in the formation of the same mixture of alcohols: Ib, IIb and IIIb.^{1,2,3}



Ia: X=NH₂
b: X=OH



IIa: X=NH₂
b: X=OH

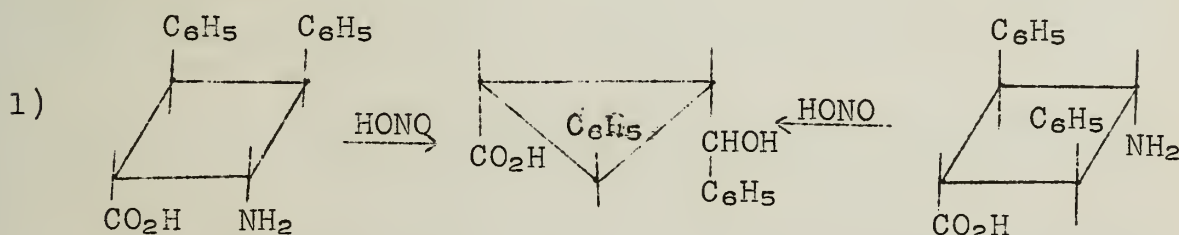


IIIa: X=NH₂
b: X=OH

This, and analogous reactions, have become of interest in the study of stereospecific syntheses and the mechanism of carbonium ion rearrangements.

Reactions

A. The first such compounds to be studied extensively were the amino acids derived from the Hofmann degradation of the mono amides of truxillic and truxinic acids.^{4,5,6} These undergo stereospecific ring contractions of the type shown in equation (1):



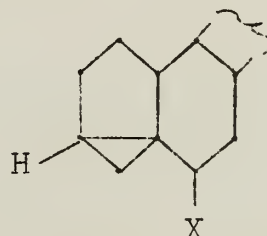
B. Cholesterol, IVa, when treated with phosphorus pentachloride or thionyl chloride, gives only cholesteryl chloride, IVb.⁷ This chloride, upon acetolysis, gives the acetate of IVa in 91% yield, with no observable epimerization.⁸



IVa: X=OH
b: X=Cl
c: X=OTs



Va: X=OH
b: X=Cl
c: X=OTs

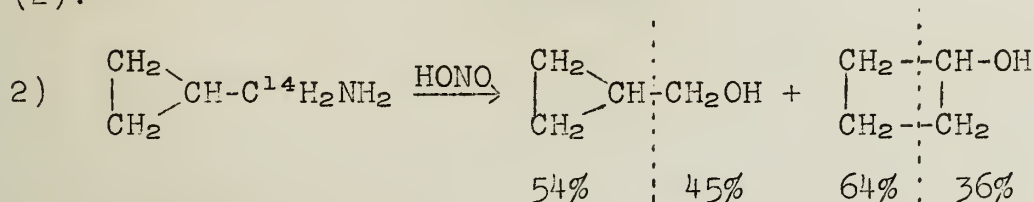


VIa: X=OCH₃
b: X=OCOCH₃

However, the corresponding saturated alcohol, Va, reacts with phosphorus pentachloride with predominant inversion of configuration at C₃ and with thionyl chloride to retain the configuration.⁹ Similarly, inversion occurs upon treatment of Vb with acetate ion. If cholesteryl tosylate, IVc, is treated with sodium acetate in methanol, the product is not the expected 3-methoxy derivative, but the i-cholesteryl ether, VIa.¹⁰ Similarly, IVc gives i-cholesteryl acetate, VIb, upon treatment with acetate ion.¹¹ Both VIa and VIb revert to the normal cholesteryl derivatives under acid conditions.

C. Solvolysis of either exo- or endo-dehydronorbornyl halides gives the same product, nortricyclyl alcohol, in better than 90% yield. This alcohol is also obtained from the solvolysis of nortricyclyl halides.¹²

D. A recent investigation by Roberts showed that either Ia or IIa, on treatment with nitrous acid, gave 48% Ib, 47% IIB, and 5% IIIB.³ The non-cyclic isomer, IIIa, led to only small amounts (ca. 13%) of Ib and IIB, but gave largely IIIB along with some crotyl alcohol and α -methallyl alcohol. Solvolysis of the tosylate of IIB in dry acetic acid gave the acetates of Ib (65%) and IIB (22%) and 13% allylcarbinyl tosylate. Rearrangement of C₁ labeled cyclopropylcarbinyl amine indicated the isotopic distribution shown in equation (2).¹³



Kinetic Data

Kinetic data of solvolysis reactions in this series have been of great help in the formulation of possible reaction mechanisms. In the simple compounds, the general order of rate constants is:^{3,14,15} cyclopropylcarbinyl > allyl > cyclobutyl > allylcarbinyl ~ s-amyl.

In the cholesteryl series, IVc is solvolyzed some 40 times faster than its saturated counterpart, Vc, while the i-cholesteryl compounds are even more reactive.¹¹

The relative rate constants for the solvolysis of the norbornyl and dehydronorbornyl chlorides in ethanol-water are:^{12,16}

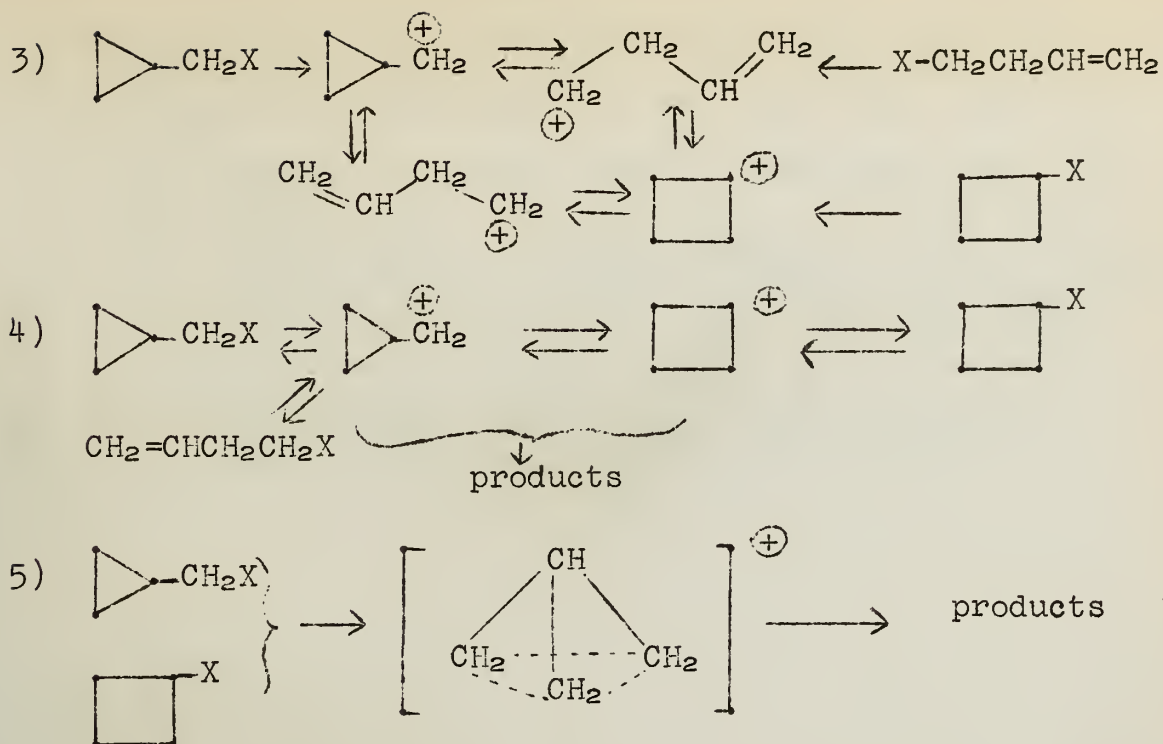
	<u>exo</u>	<u>endo</u>
Norbornyl	280	4
Dehydronorbornyl	160	1
Nortricyclyl	-- 38 --	

Mechanisms

Both Siegel⁸ and Winstein¹¹ have concluded from their kinetic data that concerted mechanisms in this series are of minor importance. There is some basis for preference among the several possible unimolecular processes which have been proposed. The first^{6,11}, equation (3) involves initial ionization followed by rearrangement. It does not take into account the following observations:

- a) driving force of the double bond in cholesterol¹⁷,
- b) products of the cyclobutyl or cyclopropylcarbinyl amine rearrangement,
- c) stereospecificity in cholesterol and truxillic acid series.

Equation (4) was proposed by Winstein¹¹ to account for the participation of the double bond in the solvolysis rate of cholesteryl derivatives. However, it is then difficult to account for the extreme reactivity of i-cholesteryl (and other cyclopropylcarbinyl) derivatives.



VII

The direct formation of a more or less symmetrical non-classical intermediate such as VII seems to be the most plausible mechanism for the rearrangements described above. By means of appropriate assumptions, none of which are unfeasible, the experimental results can be satisfactorily explained. The following details, among others, are readily justified by the assumption of such an intermediate:

- a) the equivalence of carbon atoms shown in the rearrangement of labeled cyclopropylcarbinyl amine,
- b) the stereospecificity, including the difference in rates for the isomeric dehydronorbornyl halides,
- c) the remarkable unreactivity of nortricyclyl halides.

There is some physical basis also for the plausibility of an intermediate similar to VII. Several investigators^{18,19} have shown that the electrons in a cyclopropane ring possess a high degree of polarizability, i.e. they have "more than their share" of π -bond character. Walsh²⁰ has given a molecular orbital treatment of cyclopropane which could easily be extended to formation of structures similar to VII.

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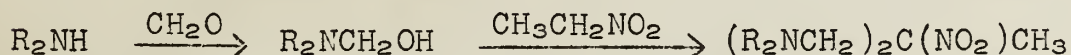
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THE MANNICH REACTION WITH NITROPARAFFINS

Reported by Bernard Freedman

December 3, 1954

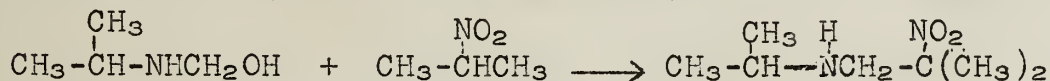
The Mannich reaction with nitroparaffins was first investigated by Henry^{1,2} who found that N-hydroxymethylpiperidine condensed with nitromethane to give 2-nitro-1,3-bis-(N-piperidyl)-propane. More generally he found:



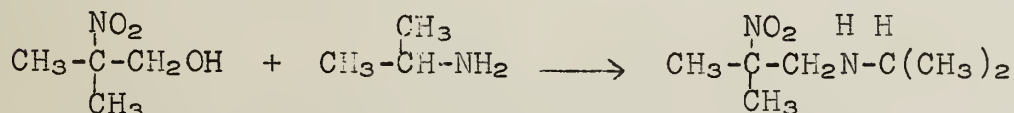
Mousset³ obtained a similar condensation between 1-nitro-3-methylbutane and N-hydroxymethylpiperidine. Zief⁷ showed that with nitroethane two moles of N-hydroxymethylmorpholine reacted whereas with nitropropane only one morpholinomethyl group was introduced. It was found that the nitro group in these products could be reduced with $SnCl_4$, thus affording a useful route to the corresponding di- or tri-amines.⁴

De Mauney⁵ postulated the rule that two moles of a N-hydroxymethyldialkylamine will react with nitromethane but with any other nitroparaffin only one mole will react. This conclusion was in contradiction to previous results, but it was later shown by Lambert⁶ that hydroxymethyl derivatives of sec-amines when heated with nitroethane and nitromethane yielded only the nitrodiamines whereas by carrying out the reaction for a short time at ordinary temperatures the monoamine was obtained.

De Mauney further believed that N-hydroxymethyldialkylamines do not react with secondary nitroparaffins and that N-hydroxymonoalkylamines do not react with either primary or secondary nitroparaffins. In order to test the validity of these beliefs Senkus⁸ treated N-hydroxymethylisopropylamine with 2-nitropropane and noted that the reaction proceeded smoothly at room temperature to give a 76% conversion to N-(2-nitroisobutyl)-isopropylamine. Senkus



further showed that this product could also be prepared in the following manner:



Presumably the nitro alcohol in the presence of the amine yields 2-nitropropane and formaldehyde. Formaldehyde and isopropylamine combine to give N-hydroxymethylisopropylamine which then reacts with 2-nitropropane as above. These two methods were found to be quite general.

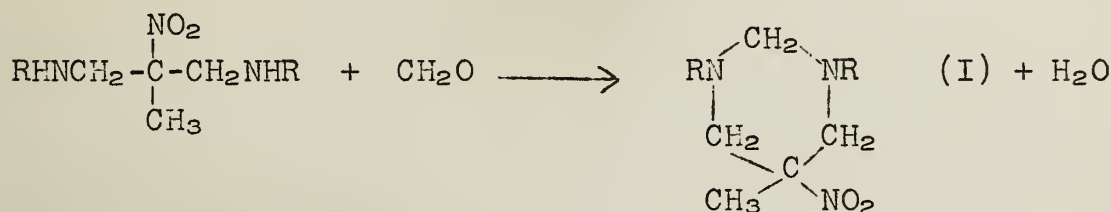
With secondary aliphatic amines, Johnson⁹ performed the reaction in two ways: (1) Reaction of the amine, formaldehyde and nitroparaffin. (2) Reaction of the amine with nitro alcohol or nitrodiol.

When aromatic amines were treated with formaldehyde and either a primary or secondary nitroparaffin, there was no

reaction until a strong basic catalyst was used to increase the ionization constant of the amine.¹⁰ Under these conditions the reaction proceeded as with aliphatic amines.

Further evidence that nitro alcohols react with amines by first splitting off aldehyde was provided by Lambert.⁶ When 2-nitro-1-propanol was treated with piperidine, disproportionation occurred which resulted in the fission of the nitro alcohol to nitroethane and formaldehyde. The aldehyde then combined with the amine to give 2-nitro-2-methyl-1,3-bis(N-piperidyl)-propane.

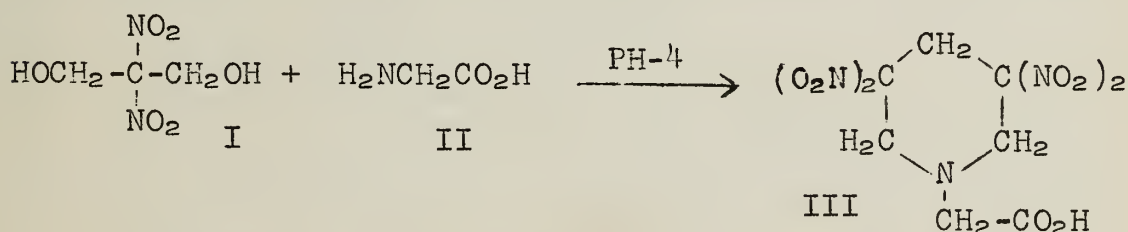
Senkus¹¹ found that 1,3-diaminopropanes reacted with formaldehyde to give cyclic 5-nitrohexahydropyrimidines.



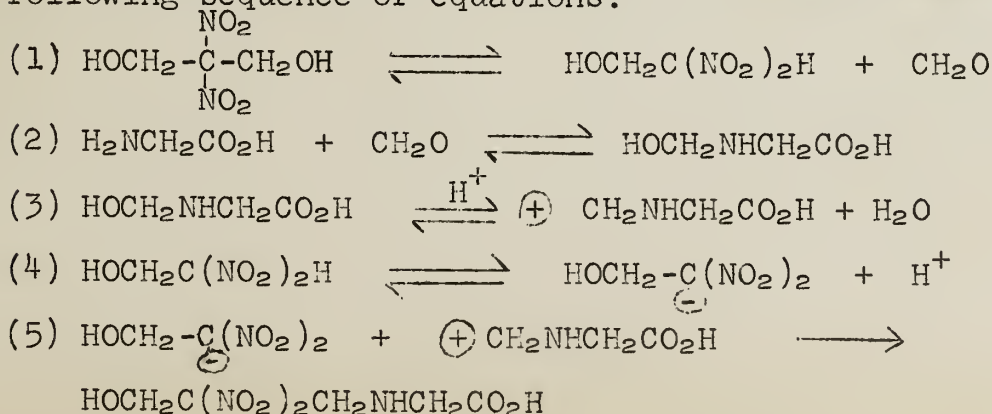
Compound I could also be prepared by the reaction of the nitrodiol, formaldehyde and primary amine, or by the reaction of the nitroparaffin, formaldehyde, and primary amine.

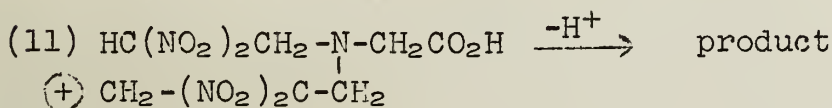
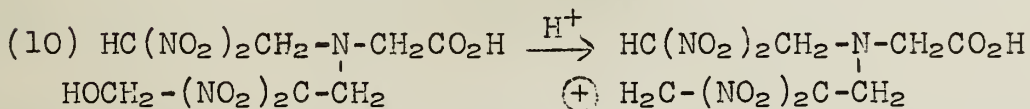
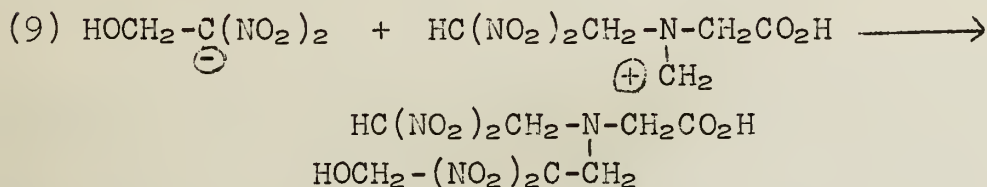
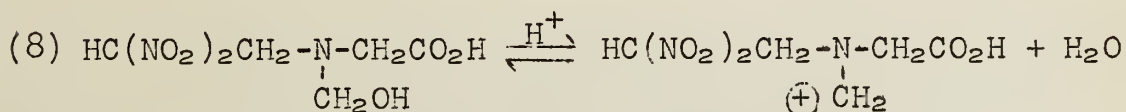
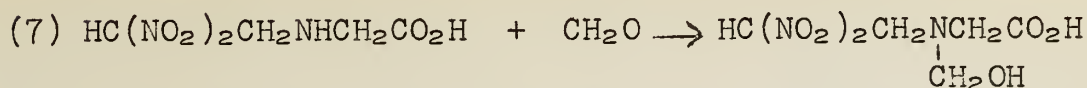
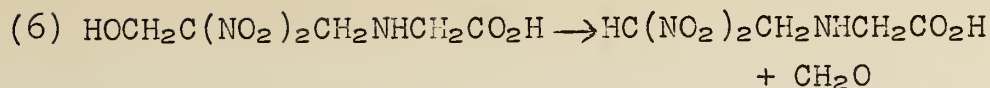
Another example involving cyclization of a nitroparaffin has been reported by Urbansky¹² who obtained a cyclic ether from the reaction of nitropropane, formaldehyde and ammonia.

Very recently the reaction between a gem dinitro paraffin and amines has been studied.¹³ Although it was expected that 2,2-dinitro-1,3-propanediol (I) would condense with two equivalents of glycine (II) to form 5,5-dinitro-3,7-diazanonanedic acid, this was not obtained. Instead 1-carboxymethyl-3,3,5,5-tetranitropiperidine (III) was formed.



The formation of the piperidine ring might involve the following sequence of equations:





Various steps in the mechanism are supported by Senkus^{8,11}, Alexander¹⁴, and Lieberman.¹⁵

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DIELS-ALDER REACTIONS OF AZODICARBOXYLIC ESTER

Reported by R. L. Pedrotti

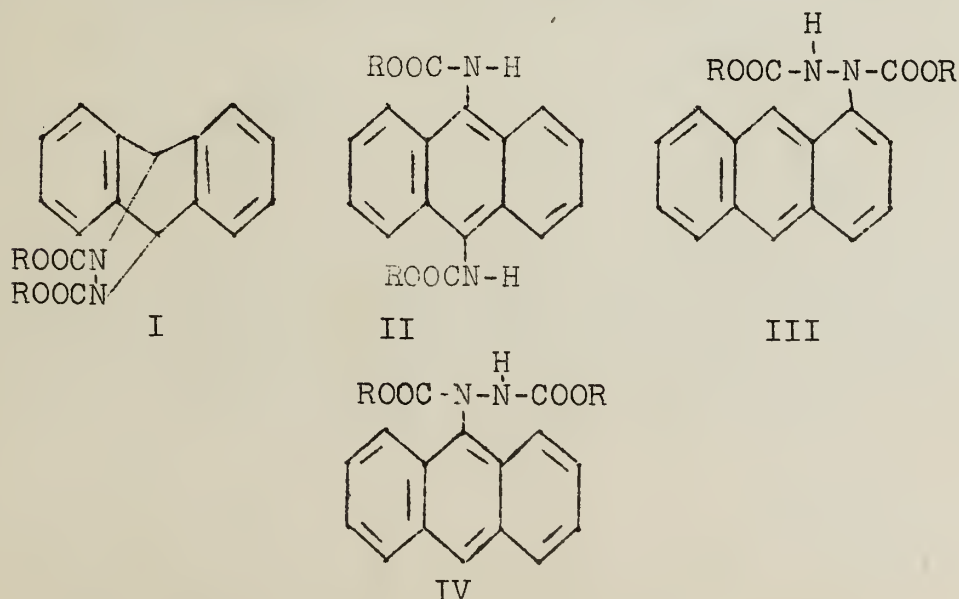
December 10, 1954

It was demonstrated in 1922 by Diels and his coworkers that azodicarboxylic ester may function as a dienophile. Typical 1,4-adducts are formed with butadiene, isoprene, cyclopentadiene and other related compounds.^{1,2}

Tetralin³ and α -methylstyrene⁴ react with the azo ester in a different fashion; attack is at the allyl position and a Michael-type addition occurs. The former type of reaction of the azo ester has been referred to as "direct addition"; the latter as "substitution addition." The behavior of the azo ester with styrene exemplifies both types of addition, a tetrahydrocinnoline derivative being formed.²

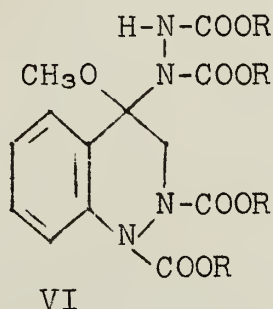
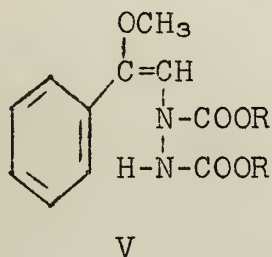
Recently Alder and his coworkers have investigated the degradation products of adducts formed by the addition of methyl and ethyl azodicarboxylate to various dienes. Some previously proposed structures have been found to be in error and new routes to the cinnolines and indoles have been found.^{8,9}

The reaction of azodicarboxylic ester with anthracene occurs at carbon atoms 9 and 10 to give a typical Diels-Alder adduct (I). I is an unstable compound but under the influence of hydrochloric acid is converted to a stable product. Diels assigned structure II to the stable product and proposed a benzidine type rearrangement for its formation.⁶ The correctness of structure II was questioned when Alder found the compound to be identical to a compound (III) reported by Stollé and Adam which had been prepared by treating anthracene and the azo ester with dry hydrogen chloride.⁷ Alder has now been able to show that neither structure II nor structure III is correct but that the compound is actually represented by a new structure (IV).⁸

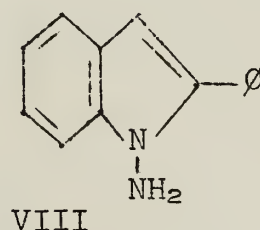
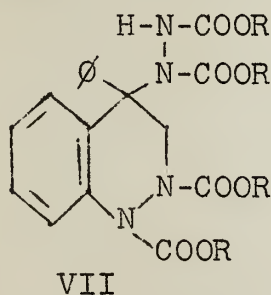


α -Methoxystyrene reacts with the azo ester to give two products (V and VI) in almost equal amounts.⁹ The formation of VI is interesting because, as in the case of styrene, both addition and substitution take place and a substituted

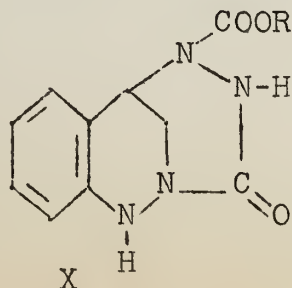
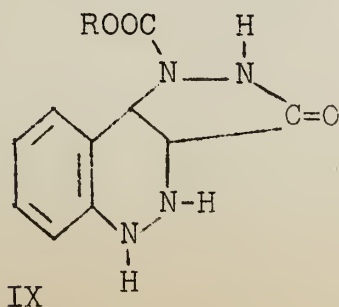
cinnoline results. Previously the only example of cinnoline formation from azodicarboxylic ester was its reaction with styrene; its reaction with α -methylstyrene, propenylbenzene, or stilbene fails to give cinnoline type compounds.¹³ Adduct VI can be converted to 4-hydrazinocinnoline by the action of hydrazine hydrate. 4-Hydrazinocinnoline can be degraded to cinnoline by the use of Cu(II) salts. This reaction corresponds to the degradation of phenylhydrazine to benzene with Cu(II) salts. According to Alder, the preparation of 4-hydrazinocinnoline by the azo ester method is simpler than previous methods. The development of compounds of the cinnoline series recently has been stimulated by the observation that certain representatives are active agents for combating malaria.¹⁰



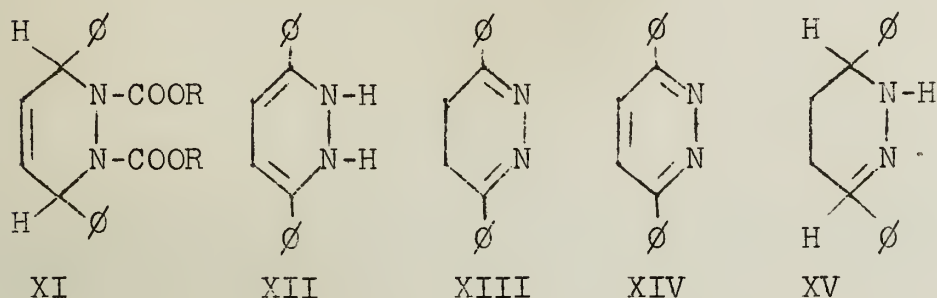
α -Phenylstyrene reacts smoothly with two moles of the azo ester to give an adduct (VII). Degradation of the adduct with hydrazine hydrate leads to N-amino-3-phenylindole (VIII) which subsequently may be reduced with platinum oxide to 3-phenylindole.⁹ This is in agreement with the findings of Neber¹¹ and Atkinson¹² who demonstrated that 4-substituted cinnolines are easily decomposed by reducing agents to ammonia and indole derivatives.



The structure of the adduct from styrene and the azo ester has been known for many years,^{2,4} however the formerly designated product IX resulting from saponification with potassium hydroxide has been shown to be in error. Alder has now assigned structure X to this compound.⁹



The azo ester reacts with trans, trans-1,4-diphenylbutadiene to give adduct XI.⁸ Dehydrogenation of XI with selenium dioxide followed by saponification with potassium hydroxide leads to an unstable base (XII) which even on recrystallization is transformed into 3,6-diphenylpyridazine (XIV). By increasing the period of saponification, a stable compound (XIII) could be isolated which is transformed into the unstable base (XII) by the addition of acid or transformed to the stable end-product (XIV) by oxidation with hydrogen peroxide. The structures for these compounds have been established as indicated.



The direct saponification of adduct XI leads to a compound which has been assigned the structure: 3,6-diphenyl- Δ^4 -tetrahydropyridazine.² Alder has now shown that the structure is actually that of XV.

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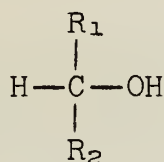
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THE STEREOCHEMICAL INTERRELATION OF TERPENES AND SUGARS

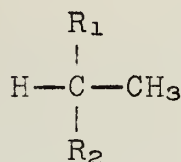
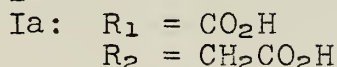
Reported by Ronald R. Sauers

December 10, 1954

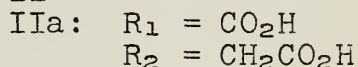
The problem of interrelating the configurations of terpenes and sugars is fundamentally one of relating asymmetric centers of type I (representing sugars) to those of type II (representing terpenes).



I



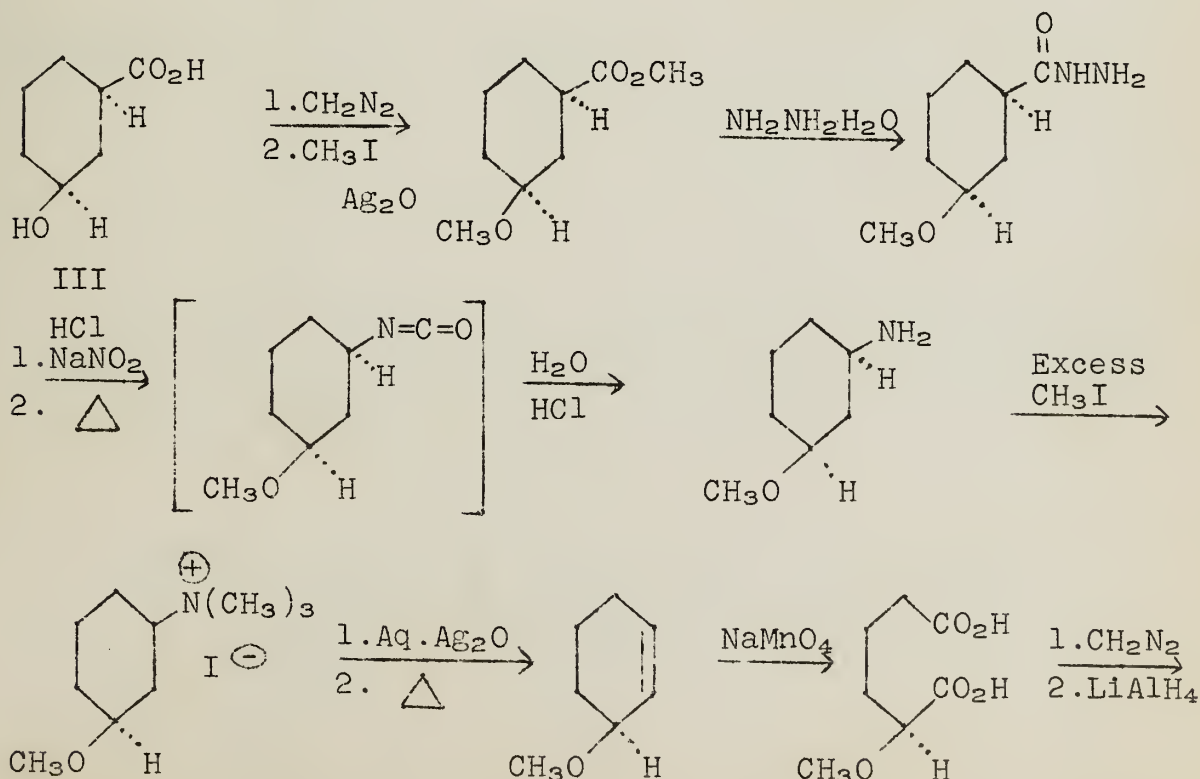
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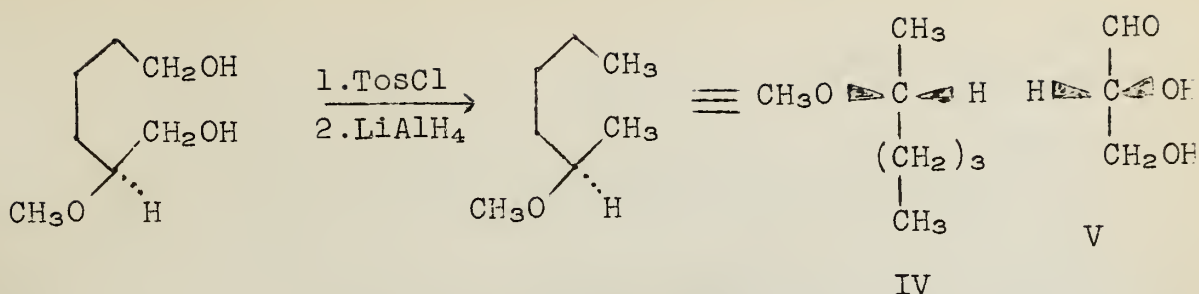


Using the method of "quasi racemates," Fredga¹ suggested such an interrelationship by showing that dextro-rotary hydroxy-succinic acid (Ia) had the same configuration as dextro-rotary methylsuccinic acid (IIa).

Calculations by Kirkwood and Eyring^{2,3} on absolute configurations are substantiated by these results.

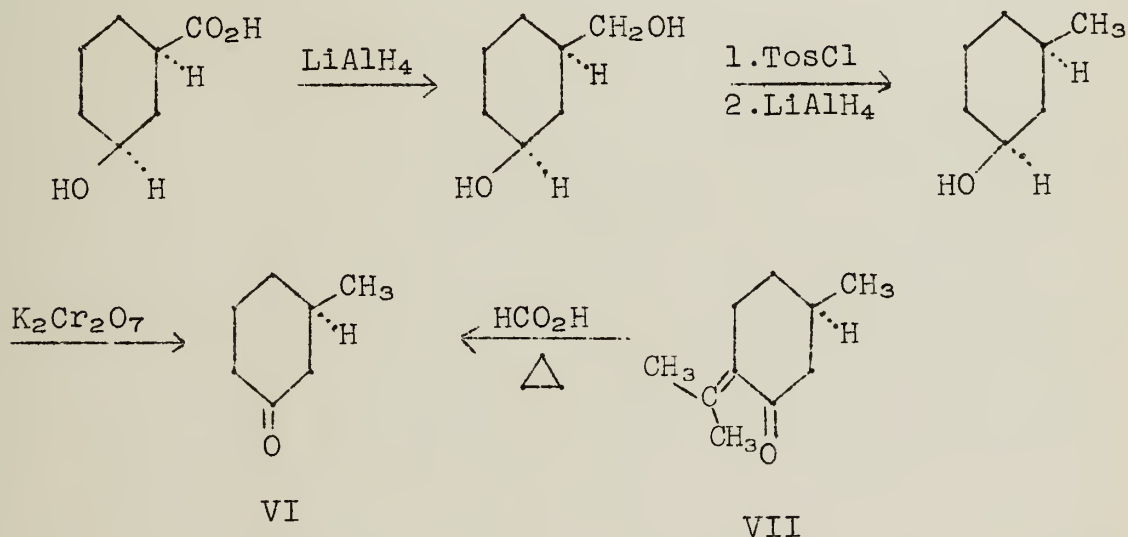
A direct chemical interrelationship has recently been accomplished through the work of Noyce and coworkers.^{4,5} Their work consisted of relating a reference compound, cis-3-hydroxycyclohexane carboxylic acid⁶ (III), to both the sugar series (via glyceraldehyde) and the terpene series (via pulegone). The following scheme was used:





The relation of (-) 2-methoxyhexane (IV) to D (+) glyceraldehyde (V) had already been accomplished by Levene and coworkers⁷. Thus the hydroxylic center of the reference compound (III) has been configurationally related to D (+) glyceraldehyde. It follows that the configuration at the carboxylic center is now also determined since OH and CO₂H are cis⁶.

It now remains only to show how the configuration at the carboxylic center can be related to the terpenes. This was done as follows^{8,9,10}:



The last reaction, the conversion of pulegone (VII) to 3-methylcyclohexanone (VI) as carried out by Wallach¹¹, serves to correlate many monocyclic terpenes as summarized in schemes assembled by Huckel and Birch¹².

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CHEMICAL STRUCTURE AND CARCINOGENIC ACTIVITY

Reported by Paul Tombouliau

December 17, 1954

CARCINOGENIC SUBSTANCES

The production of malignant tumors in animal tissues by the application of chemical agents was first demonstrated about 40 years ago¹. The high incidence of cancer among employees in the coal tar and aniline dye industries led eventually to the separation and identification of carcinogenic compounds²⁻⁶.

The large majority of the known compounds found to be carcinogenic in test animals⁷ fall into two groups: (1) polynuclear aromatic hydrocarbons and their isologs and (2) a smaller group of aromatic amino compounds. Most of the hydrocarbons are derivatives of phenanthrene or anthracene, although these parent compounds are inactive. The simplest known of these hydrocarbons are 1,2,3,4-tetramethylphenanthrene and 9,10-dimethylantracene⁸. Of the six possible unsubstituted tetracyclic hydrocarbons, only 3,4-benzphenanthrene is active. In general, methyl substituents in certain positions cause increased activity, although the effect of other substituents is variable^{9,10}. Di- and trimethyl derivatives of certain tetracyclic compounds are among the most potent carcinogens known; some of the di- and trimethyl nitrogen isologs, the benzacridines, are also active. Of the higher cyclic compounds, the following are active: 1,2,5,6- and 1,2,7,8-dibenzanthracene; 1,2,3,4- and 1,2,5,6-dibenzphenanthrene; 1,2,3,4- and 3,4,8,9-dibenzpyrene; 3,4-benzpyrene; and 1,2,5,6-, 1,2,7,8-, and 3,4,5,6-dibenzacridine. Dibenzocoronene and graphite are both inactive¹¹.

Substituted aminoazobenzenes and aminostilbenes compose most of the second group of active compounds, on which much less work has been done. Here, also, the amount and type of substitution appear to play an important role. For example, although 4-aminoazobenzene and 4-dimethylamino-2'-methylazobenzene are inactive, 4-dimethylaminoazobenzene is active¹².

CORRELATIONS

The carcinogenic activity of polynuclear hydrocarbons does not correspond with their reactivities toward electrophilic agents^{10,13}. On the other hand, almost all of these carcinogens contain the phenanthrene nucleus, and therefore the highly reactive 9,10 bond or "K region" appears to be a likely position for reaction. Robinson¹⁴ suggested that the action of a carcinogen was due to a 9,10-phenanthrene-type bond activated by electron donor groups on the ring.

Calculations and experimental results have supported this view¹⁵⁻¹⁸. Schmidt was first to propose that carcinogenic activity results from the effect of a region of high π electron density in the molecule. Applying quantum mechanical methods, A. Pullman^{13,16,19-22} has calculated a number of electronic indices for aromatic systems, showing that the K region does possess special properties. In spite of the approximations used, these indices correlate well with the carcinogenic activity of the compounds. Similar calculations for azo

compounds indicate that the azo bond (K' region) is similar in many respects to the K region of hydrocarbons^{23,24}.

Experimentally determined indices using double bond reagents have higher correlations with carcinogenic activity than have the theoretical indices. Badger has employed these reagents on polynuclear hydrocarbons^{25,26}. He found that osmium tetroxide complexes are formed at a rate which corresponds closely to their relative carcinogenic activities. Badger has also used perbenzoic acid to determine the relative electron density of the azo linkage in various azo compounds^{12,27}. He demonstrated a relation between the rate of oxidation and the activity of these compounds. Kofahl and Lucas²⁸ have found an excellent correlation between argentation constants and carcinogenic activity.

Carcinogenic activity is apparently influenced, however, by more than one factor. The size, shape, and planarity of a molecule have marked effect on its potency as a carcinogen⁹. Druckrey²⁹ has suggested that carcinogenic activity is chiefly a function of the basicity of the molecule.

MECHANISM OF REACTION^{9-14,17,22,30-32}

The physiological action of a carcinogen may first involve the formation of an addition complex between the K or K' region and a cellular receptor such as an enzyme. This complex may eventually affect cell growth or produce some chromosomal abnormality. This view is supported by: (1) the inhibition of carcinogens by structurally similar noncarcinogens³³, (2) the existence of azo dye-protein³⁴ and 3,4-benzpyrene-protein complexes³⁵, and (3) the isolation of *in vivo* oxidation products in which the phenolic groups occupy positions other than the K region^{17,36}.

Individual differences between closely related carcinogens may be due to steric factors, metabolic conversions, hydrogen bonding, and solubility.

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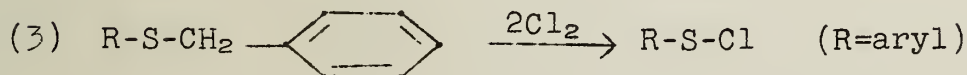
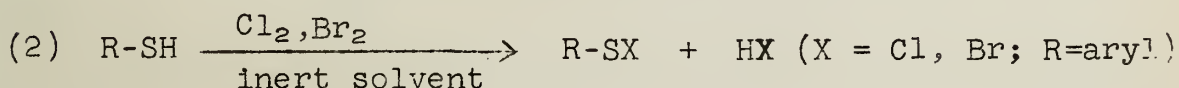
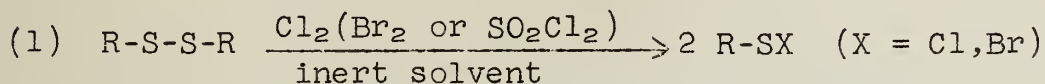
SULFENIC ACIDS AND THEIR DERIVATIVES

Reported by Charles A. Plantz

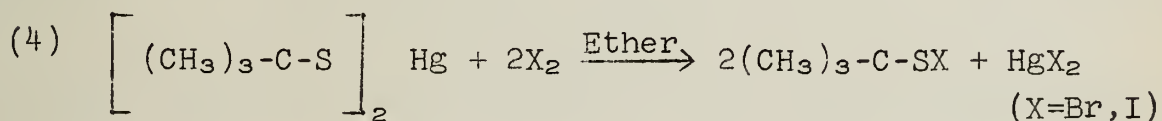
December 17, 1954

Sulfenic acid derivatives are compounds with the general formula R-SX where X may be -OH (acids), -NR₂ (amides), -OR (esters) OSR (anhydrides), SCN (sulfenyl thiocyanate) or halogen. Only one example of a free sulfenic acid is known, but many examples of the other derivatives are known.

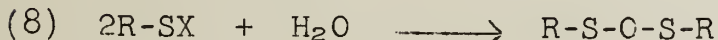
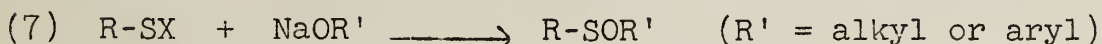
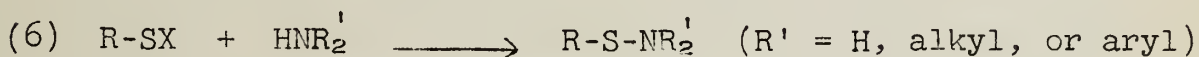
Most of the sulfenic acid derivatives are made from the halides, which are synthesized as follows:



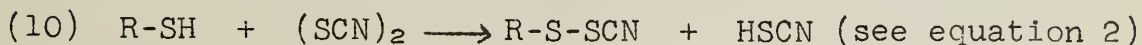
Special Cases:



The other sulfenic acid derivatives are synthesized from the halides as follows:

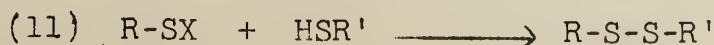


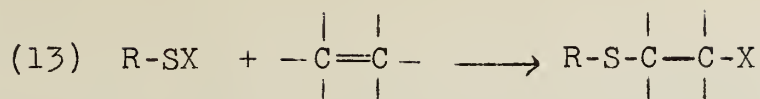
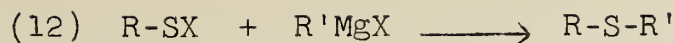
The sulfenyl thiocyanates can be synthesized according to:



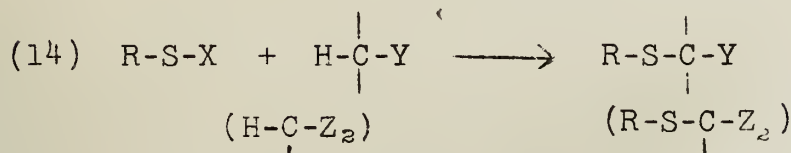
and can be used in place of the halides in equations 6, 7, 8, 11, 13 and 14.

Other reactions of the halides are:





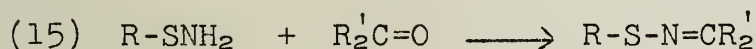
Reaction with active methylene compounds



(where Y = carbonyl or nitro Z = carbonyl or carboxyl)

Reaction (13) has been suggested as a method of making derivatives of olefins since the halosulfides formed can be oxidized to sulfones.

An interesting reaction of sulfenamides is the formation of derivatives similar to Schiff's bases.



Sulfenamides have been used extensively as vulcanization accelerators by the rubber industry and also as oil antioxidants, antifungal agents, and insecticides. Sulfenyl chlorides are used as insecticides and for making resins.

Some derivatives of selenenic acids have been made (R-SeOH) which are quite similar to the corresponding sulfenic acid derivatives.

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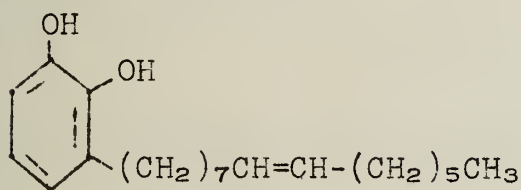
POISON IVY "URUSHIOL"

Reported by William G. DePierri, Jr.

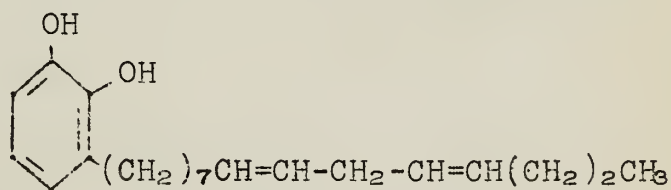
January 7, 1955

The toxic principle of the poison ivy plant (*Rhus toxicodendron radicans*) and of the related species poison oak (*Rhus toxicodendron diversilobum*) and poison sumac (*Rhus toxicodendron vernix*) have interested investigators^{1,2,3} for many years. Early attempts by McNair^{4,5} to determine the structure of the poisonous principle led to the conclusion that the toxic properties of the plant were caused by a compound or compounds possessing a catechol nucleus with an unsaturated side chain. Later, Hill and coworkers⁶ demonstrated that the hydrogenated form of the substance was identical with hydro-urushiol, the saturated analog of the vesicant oil occurring in the sap of the Japanese lac tree. Earlier, Majima⁷ had identified hydro-urushiol as 3-pentadecyl catechol. However, they were unable to determine the position of the olefinic linkages in the side chain. Chromatography of the vesicant⁸ led to the conclusion that it was a mixture of at least three toxic components.

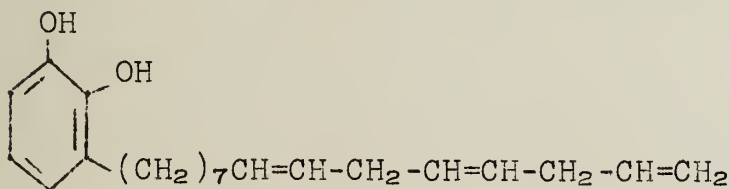
Symes and Dawson⁹ isolated four compounds from an extract of the poison ivy plant which they concluded were responsible for the toxic nature of the plant. The compounds, which were found to be the same except for the degree of unsaturation in the side chain, were identified as a monolefin (I), a diolefin (II), a triolefin (III), and a saturated analog (IV). The compounds were separated chromatographically and structures



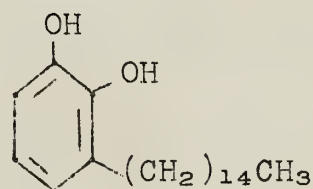
I



II



III



IV

were assigned by utilization of evidence obtained by a combination of degradative and spectral analysis.

It is of interest to note that the type of compounds in poison ivy "urushiol" is closely related to the structure of irritants from other natural sources. The side chain structures of the mono-, di- and triolefinic components of poison ivy "urushiol" are the same as those of the corresponding olefinic components of cardol, cardanol and anacardic acid, mixtures which constitute the major portion of cashew nut shell liquid^{10,11}.

Some attempts^{12,13,14} have been made to correlate the structure of these and related compounds with their physiological activity. It has been found that both shortening the side chain and decreasing the degree of unsaturation of the side chain decrease the toxic character of the substances. Hydroxyl groups meta to the side chain appear to be necessary if the compound is to be toxic, whereas ortho or para hydroxyl groups tend to diminish the activity. Conversion of phenolic groups to methyl ethers eliminates or greatly reduces the activity of the compounds.

On the other hand, there has been little success in determining the reason for the characteristic poison ivy reaction. It is believed that the vesicant enters the body by dissolving in the lipid components of the skin¹². This would explain the effect of length of side chain upon toxicity.

Apparently, the reaction is not simply a burn caused by the phenolic substances, since it has been found that an initial exposure is required to sensitize an individual. The sensitivity diminishes if exposure is not repeated for long periods of time¹⁵. Also some persons are quite sensitive to the irritating effects, while others are naturally immune. One theory¹⁶ to explain immunity postulates the presence in the skin of immune individuals of larger amounts of polyphenolase (an oxidase) which renders the vesicant harmless by oxidation of the sensitive catechol nucleus. There have been attempts¹⁶ made to relate susceptibility to poison ivy with skin color, but the work has not been conclusive except in the case of guinea pigs.

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THE OXIDATION OF PRIMARY AROMATIC AMINES BY PHENYL IODOSOACETATE

Reported by Eiichi Tanda

January 7, 1955

It has been shown by Criegee et al¹ that aryl iodoso acetates², like lead tetraacetate, can oxidize unsaturated compounds and can bring about the fission of 1,2-glycols. Pausacker et al³ studied the oxidation of aromatic primary amines in benzene solution and in acetic acid at room temperature.

In general, meta aryl amines and the negatively substituted amines gave better yields of azo compounds upon oxidation. For example, 2-nitro-4-chloro-aniline gave 32% of the corresponding azo compound, and 2-nitroaniline gave 23% of the azo compound. The azo compounds were separated by chromatography.

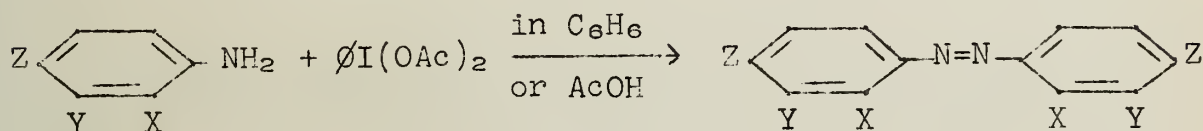
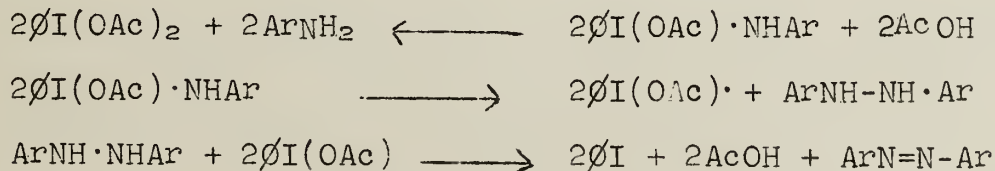


Table I - Yield of Azo Compounds

	% in C ₆ H ₆			% in CH ₃ COOH		
	X,Y=Z=H	Y,X=Z=H	Z,Y=X=H	X,Y=Z=H	Y,X=Z=H	Z,X=Y=H
NO ₂	---	95	53	23	61	63
Cl	39	66	55	25	34	24
H	95			0		
CH ₃	42	56	6	---	---	---
OC ₂ H ₅	---	---	7	---	---	---
OCH ₃	3	---	5	1	---	4

Pausacker suggested that the azo compounds are formed as follows:



Although hydrazobenzene could be oxidized to azobenzene in benzene or acetic acid almost quantitatively, no identifiable oxidation product was obtained from aniline in acetic acid solution. It would seem then that aniline is not initially oxidized to hydrazobenzene in the manner postulated by Pausacker.

When o-nitroaniline derivatives were oxidized in benzene, benzofurazan oxides were formed.

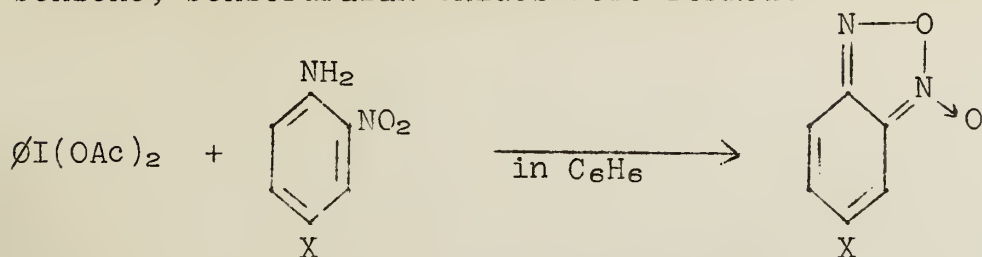
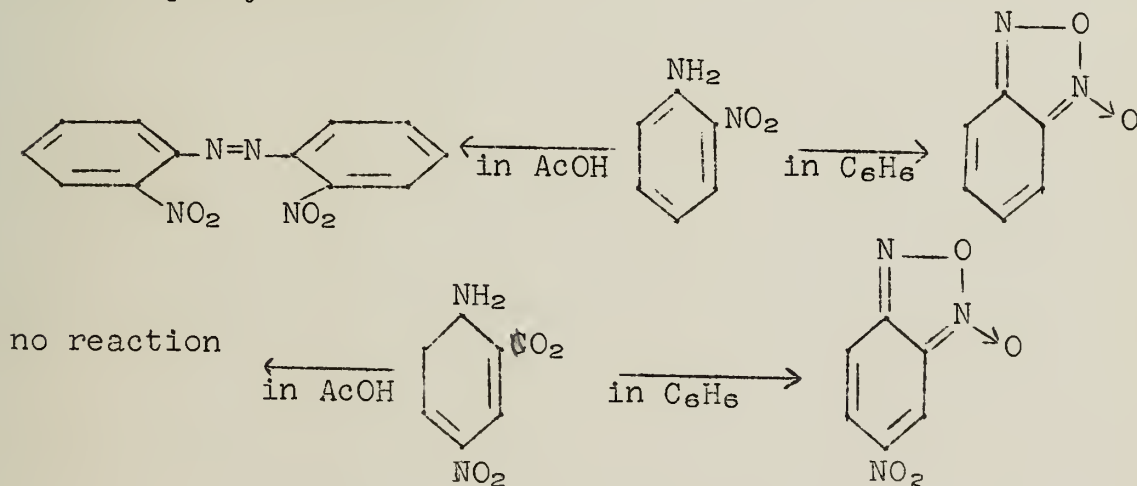


Table II - Yield of Benzofurazan Oxides

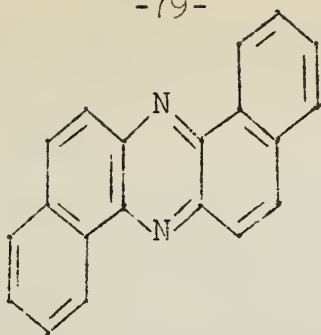
X	H	CH ₃	Cl	NO ₂
Yield	81%	96%	91%	94%

Green and Rowe⁴ have reported that o-nitroaniline is converted into benzofurazan oxides by alkaline sodium hypochlorite but into the corresponding azo-compound under neutral conditions. Similar phenomena were observed in the case of phenyliodosoacetate.



When β -naphthylamine was oxidized in benzene, it formed 1,2,6,7-dibenzophenazine (28%) A and a product, $\text{C}_{25}\text{H}_{20}\text{O}_5\text{N}_2$, which has a green metallic luster, gives a deep blue solution in nitrobenzene and resembles the compound obtained by Liebermann on oxidation of β -naphthylamine with ferric chloride. In acetic acid, β -naphthylamine gave an unexpected result. No 1,2,6,7-dibenzophenazine was isolated. The principle products were 2-acetamido-1,4-naphthoquinone (up to 34%) and 2-acetamido-1,4-naphthoquinone-1- β -naphthylimide (25%).

A



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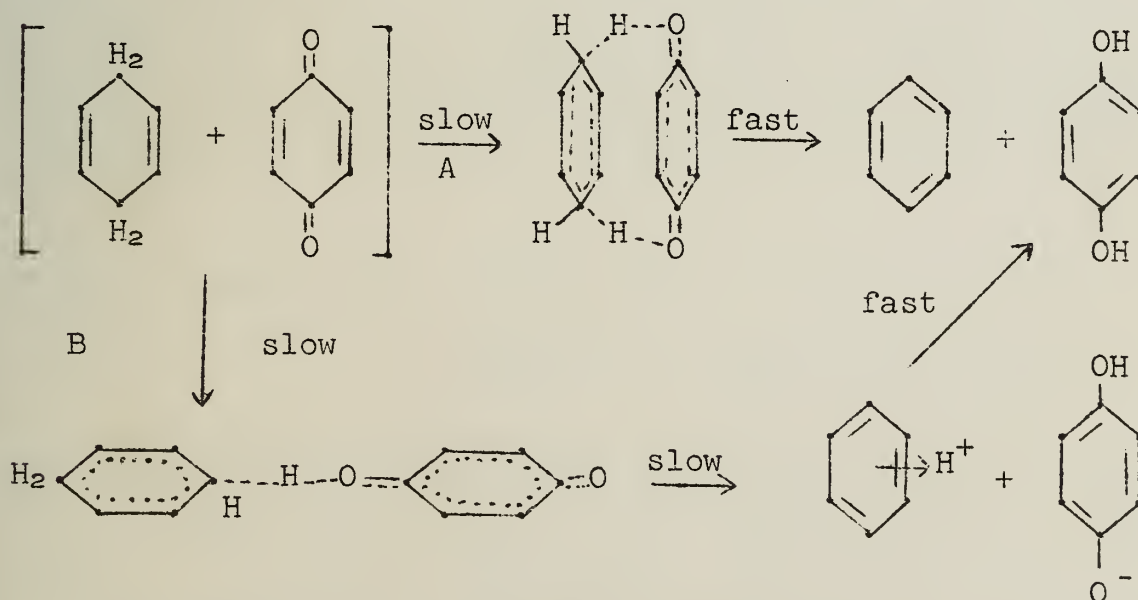
MECHANISMS OF THE DEHYDROGENATION OF DIHYDROAROMATIC COMPOUNDS BY QUINONES

Reported by Richard C. Thamm

January 14, 1955

The dehydrogenation of certain dihydroaromatic compounds by various quinones is of considerable synthetic value, but until the recent publications of Braude, Linstead, Jackman and Brook^{1,2,3,4} little was known concerning the mechanism of this process. Several workers^{5,6} have suggested that the reaction may proceed by a homolytic removal of hydrogen atoms from the donor molecule. Although none of the data thus far accumulated precludes this possibility, such a mechanism is not generally accepted because of the lack of catalysis by peroxides or ultraviolet light and because of the absence of coupling products.

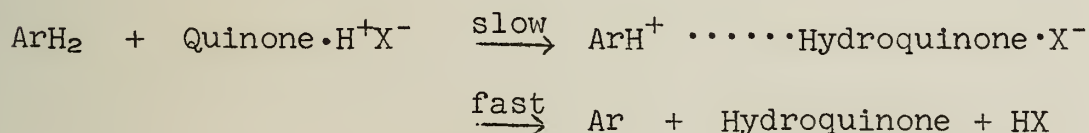
The rates of the reactions between various quinones and 1,4-dihydronaphthalene have been measured in phenetole solvent at 140°. It was found that strict second order kinetics were followed, and hence the process is probably bimolecular. On the basis of this information alone it is possible to postulate two mechanisms: (A) simultaneous transfer of both hydrogen atoms from the donor to the acceptor by a "covalency exchange" type process and (B) rate controlling displacement on hydrogen by the quinone, giving the conjugate base of the quinone and the protonated aromatic compound. The charged intermediates of mechanism B are considered by Braude and Linstead³ as existing in the form of an ion pair.



There appears to be a nearly linear relationship between the free energy of activation for the hydrogen exchange reaction and the ΔF change for the equilibrium "quinone \rightleftharpoons hydroquinone" (as determined by the standard electrode potential, E^0). A standard donor (1,4-dihydronaphthalene) was treated with variously substituted quinones: mono-, di-, tri- and tetrachloro-1,4-benzoquinone, mono- and dimethyl-1,4-benzoquinone, thymoquinone and 1,4-naphthoquinone. A plot of ΔF^\ddagger against E^0 for this series was nearly linear for the methyl quinones, with some deviation in the cases of the chloroquinones. Such

linearity may be taken to mean that the transition state for the hydrogen exchange reaction resembles hydroquinone, in that there is little negative charge on oxygen. The mechanism postulated for A, but not for B, is consistent with this argument.

Solvent effects are small. At 100° the rates are nearly identical in decalin and phenetole for the reaction between thymoquinone and 1,4-dihydronaphthalene. There was only a fivefold increase in going from phenetole to dimethyl formamide for the same reaction at 140° in phenetole and 9/1 propionic acid-water solvents there was only a fourfold increase in the rate. Reactions involving ion pairs, such as the thermal decomposition of secondary alkyl chlorosulfites⁷ (relative rates in isooctane, toluene and dioxane: 1/1.5/330) and the rearrangement of perbenzoate esters⁸ (relative rates in benzene and acetic acid: 1/50,000) show a much greater dependency of rate upon solvent. On the other hand, the rate of the ortho Claisen rearrangement⁹ is not appreciably affected by the addition of either dimethylaniline or acetic acid to the reaction mixture (less than a 10% change in k_1). These data can be taken as good evidence for mechanism A. Braude and Linstead^{2,3} have demonstrated that the reaction can be catalyzed by the action of strong acids such as perchloric acid, where the rate of the reaction is increased by a factor of 1000, employing propionic acid as the solvent. While it cannot be inferred that the uncatalyzed reaction proceeds via the same mechanism, it seems likely that this process may involve ionic transfer as indicated below. However, addition of weaker acids such as trifluoroacetic or picric acids only increase the rate by a factor of two or three. This change may well result from medium changes and not general acid catalysis.



It should be mentioned that quinones or donors incapable of passing through a transition state such as that postulated in A, do react, providing that the quinone possesses a high enough electrode potential. Thus, 1,8-diphenoquinone will react with 1,4-dihydronaphthalene², and 1,1-dimethyltetralin is dehydrogenated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone¹⁰. These reactions may proceed by a mechanism similar to B (the second reaction would presumably involve rearrangement of the partially dehydrogenated donor carbonium ion).

It therefore appears that there are at least four possible mechanisms for the hydrogen exchange reactions between quinones and partially reduced aromatic compounds: (1) a free radical process which is deemed unlikely, (2) an uncatalyzed reaction

involving the simultaneous shift of both hydrogens from the donor to the acceptor, (3) an acid catalyzed reaction involving the conjugate acid of the quinone and (4) a possible displacement on hydrogen when the reactants are structurally unable to form a cyclic, uncharged transition state.

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SEMINAR TOPICS

CHEMISTRY 435

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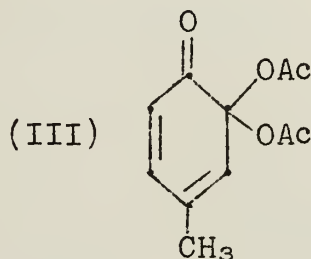
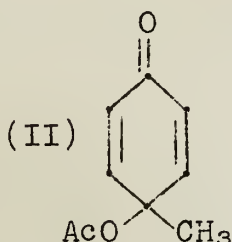
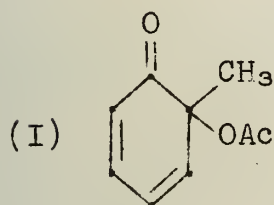
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THE REACTION OF ORGANOMETALLIC COMPOUNDS WITH QUINOL ACETATES

Reported by S. J. Strycker

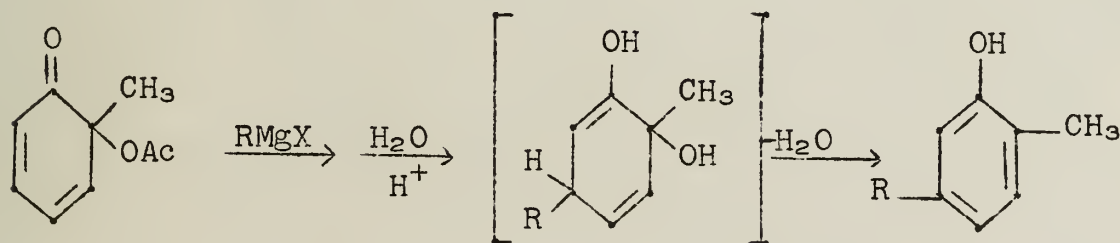
February 11, 1955

Quinolins have been known since the turn of the century,^{1,2,3} but, because of the lack of suitable methods of preparation, relatively little work has been done on them. Recently a promising method of preparation has been discovered which involves the reaction of lead tetraacetate on phenols.^{4,5} Illustrative of the new types of quinol acetates made available through the application of this method are the following:



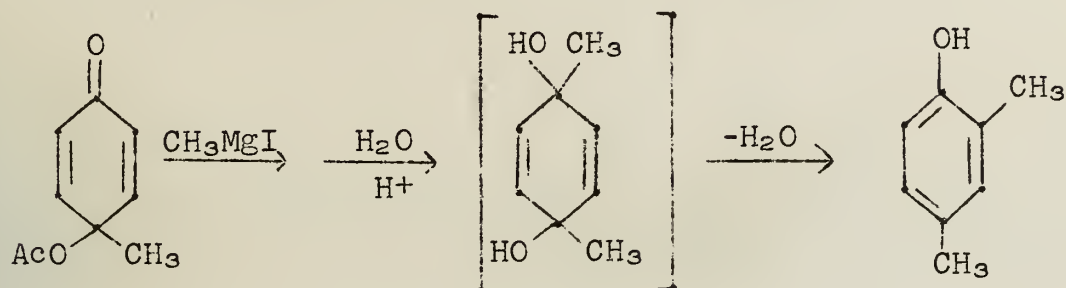
Ortho quinols in fact had not previously been reported in the literature. The structures of these quinols have been established by ultraviolet spectroscopy, catalytic hydrogenation, and quantitative analysis. Many quinols have been prepared by other methods,^{6,7} but the lead tetraacetate procedure is vastly superior. The reaction undoubtedly proceeds by way of a free radical mechanism.

Both ortho and para quinols contain an α,β -unsaturated carbonyl system which offers the possibility of 1,4-addition of a Grignard reagent.⁸ In spite of the rigid position in which the conjugated system is held, Grignard reagents have been found to add to I in the 1,4-manner. In some instances reduction has been observed. Phenyllithium also added 1,4 readily.

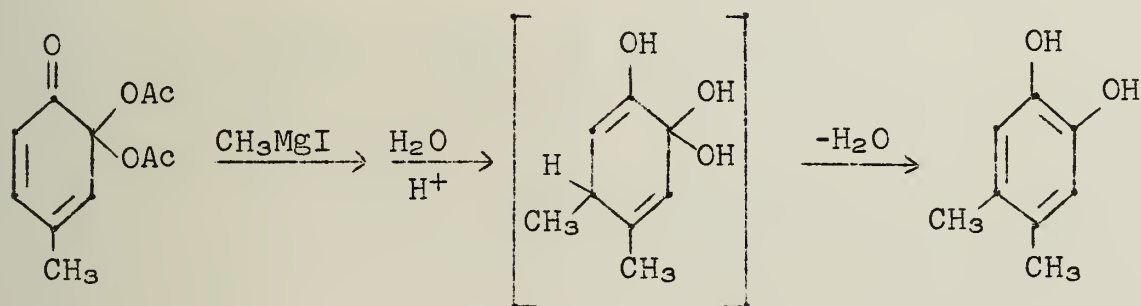


Products obtained from the para quinols have been found to behave in a way which is especially interesting. To explain the reaction of II, for example, with Grignard reagents, the postulation has been made that 1,2 addition occurred followed by subsequent migration of one of the alkyl or aryl groups.

The postulated intermediate diol from the phenyllithium reaction was actually isolated and characterized.⁹



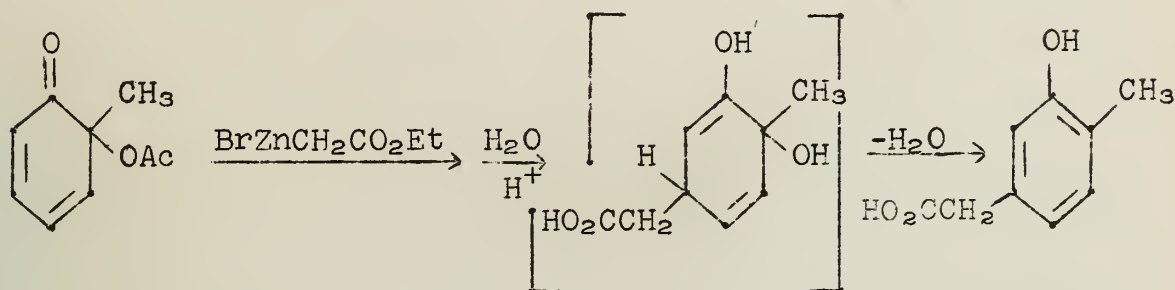
The following example shows that III also undergoes conjugate addition:¹⁰



The investigation has been extended to organozinc compounds in a strikingly novel way.¹¹ When zinc, a bromoester and I were brought together in the customary Reformatsky procedure, the zinc reduced the *o*-quinol, and the product was *o*-cresol. For a successful reaction the preparation of the Reformatsky reagent as such in solution seemed to be necessary. This organozinc compound had previously been prepared in the absence of the carbonyl component of the Reformatsky reaction, but the method set forth was not practical.¹²

In the search for a better procedure the following factors were found to be important: time of reaction, solvent, catalyst and form of zinc. The reagent was prepared by adding zinc powder to an absolute ether solution of ethyl bromoacetate. Methylmagnesium iodide was found to be the best catalyst. For optimum results the reaction was allowed to proceed for 90 minutes, after which the ether solution of the organozinc reagent was decanted from the oil which formed and from any unused zinc. When the Reformatsky reagent, so prepared, was allowed to react with benzophenone, the product is the same as that obtained by the regular procedure. The preformed Reformatsky reagent, however, gave a 10% better yield. The reaction of this reagent with I proceeded in the 1,4 manner. This type of addition has been observed only rarely with

Reformatsky reagents. This is the only known example of conjugate addition involving ethyl bromoacetate.¹³



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NON-IONIC ELIMINATION REACTIONS

Reported by Frederick H. Owens

February 11, 1955

Non-ionic elimination reactions* have become of increasing importance because they lead to olefins with unaltered carbon skeletons and are frequently stereospecific.

Three general mechanisms for these reactions have been postulated:³

1. Heterogeneous decomposition (on the walls of the reactor). This reaction is normally much faster than the other two mechanisms, and since it can be reduced to insignificance by coating the reactor with a carbonaceous film, it will not be considered in detail here.

2. Homogeneous radical-chain decomposition.

3. Homogeneous unimolecular decomposition. It must be emphasized that the word "unimolecular" means that only one molecule is present in the transition state.

The following criteria have been established for determining which mechanism is operative:

1. A reaction is homogeneous if changing the ratio of surface area to volume does not cause an appreciable change in the rate.^{4,5}

2. A radical-chain mechanism, but not a unimolecular mechanism, will exhibit a reproducible induction period, which is dependent on the temperature and the initial pressure. This induction period has been shown to be the time required to build up a steady-state concentration of the chain-carrying species.^{4,5,6}

3. A radical-chain mechanism, but not a unimolecular mechanism, will be inhibited by the addition of small amounts (ca. 0.5%) of propylene or nitric oxide and will be accelerated by the addition of small amounts of chlorine or oxygen.^{4,5,6}

4. In the homogeneous, unimolecular reactions thus far studied, the non-exponential term "A" in the relevant rate equation $k = Ae^{\frac{-E}{RT}}$, is generally within a power of 10 of 10³.

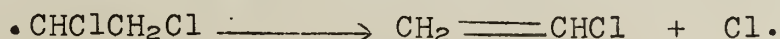
Radical chain reactions usually differ from this value by 10¹³ fold.⁵

5. Ramsperger's criterion is that for a unimolecular reaction, there exists a critical pressure region below which the Maxwell-Boltzmann distribution of energies is not maintained, manifesting itself in a lowering of the rate constant and a change towards second order kinetics.^{7,8,9}

The homogeneous radical-chain mechanism is envisaged as a four step process¹⁰ here exemplified by 1,2-dichloroethane:⁴

a. Initiating step or steps which lead to the production of chlorine radicals.

b. Propagation steps:



*Reactions which are believed not to have ionic transition states; for instance, Barton has pointed out that pyrolysis of potassium bornyl sulfate is an ionic reaction.¹ Also the pyrolysis of sulfite esters may involve ionic intermediates.²

c. Termination step:

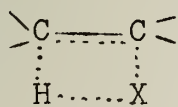


A compound will decompose by a radical-chain mechanism only so long as the compound itself, the reaction intermediates, or the reaction products are not inhibitors for the chains.^{4,10} Typical inhibitors are propylene, saturated hydrocarbons, isobutene, menthene, and acetaldehyde. Ethylene, vinyl chloride, vinylidene dichloride, trichloroethylene, 1-chloropropane, and divinyl ether do not inhibit radical-chain reactions.¹¹

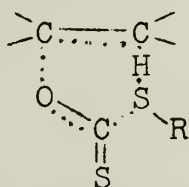
The decomposition of ethyl chloride is a case in point. The first propagation step is the abstraction of a hydrogen atom by the chlorine radical. From the vapor phase chlorination of ethyl chloride, it has been shown that the hydrogen attached to carbon 1 is most easily removed; however, the 1-chloroethyl radical cannot eject a chlorine radical unless a hydrogen atom is shifted from carbon 2 to carbon 1; therefore, the radical formed inhibits its own radical-chain decomposition, and this elimination proceeds exclusively via the unimolecular mechanism.^{4,10} *t*-Butyl chloride is not an inhibitor, but the isobutene formed by the reaction is an inhibitor, and thus, the reaction does not go by radical-chain mechanism.¹⁰

However, it must be emphasized that this rule of structure is a negative one, for it merely states that compounds of certain types cannot proceed by radical-chain mechanism, it does not state that because a compound can decompose by a radical-chain mechanism that it will do so.

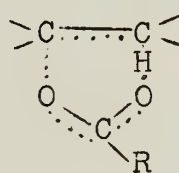
Elimination reactions of the unimolecular type involving halides and alcohols might be expected to proceed through a cis, four-centered, planar transition state (I).^{12,13} It has been suggested that the thermal decompositions of xanthates and esters are unimolecular reactions proceeding through transition states of the types shown below:^{3,14,15}



I



Xanthates



Esters

Granted this, then cis stereochemistry for the reaction follows. However, no theoretical conclusions as to the stereochemistry of elimination reactions are justified until it is proved that the reaction is homogeneous and unimolecular.³

Barton has shown that the pyrolyses of (-) menthyl chloride³ and benzoate¹⁶ fulfill the criteria of unimolecularity. O'conner and Nace showed that the pyrolysis of β -cholestanyl-S-methyl xanthate and cholesteryl-S-methyl xanthate are homogeneous, unimolecular reactions.¹⁷ By analogy, it is reasoned that all pyrolyses of xanthates and

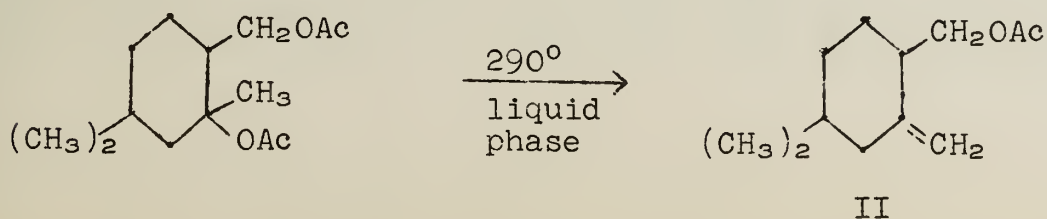
esters are homogeneous, unimolecular reactions producing cis elimination. However, a generalization of this type is invalid as is shown by the work of Cram,¹⁸ Alexander and Mudrak,^{19,20} and others.^{21,22}

When Alexander and Mudrak pyrolyzed methyl (+) neomenthyl xanthate, they obtained 20% of cis-3-menthene(trans elimination) and 80% of 2-menthene.¹⁹ Pyrolysis of methyl cis-2-methyl-1-indanyl xanthate produced 20% of 2-methylindene and pyrolysis of the acetate produced 10% of the product resulting from trans elimination.²⁰ In the pyrolysis of the xanthates of the diastereomeric 3-phenyl-2-butanols and 3-phenyl-2-pentanol, Cram observed a slight amount of trans elimination which he attributed to an intermolecular reaction.¹⁸

In considering the direction of elimination, it is necessary to distinguish between acyclic systems, cyclic systems where only endocyclic elimination is possible, and cyclic systems where exocyclic elimination is possible. In pyrolysis of halides, alcohols and xanthates of the acyclic series, few quantitative data are available; therefore, no definite rules for the direction of elimination have been established. Recently, Bailey has shown that the pyrolysis of acetates follows the Hofmann rule exclusively.^{23,24} Thus, the pyrolysis of t-amyl acetate yields only 2-methyl-1-butene,²⁴ whereas the pyrolysis of the chloride or alcohol produces a mixture of 2-methyl-1-butene and 1-methyl-1-butene.^{25,26} However, before any definite rules can be laid down, further work is necessary to substantiate the fact that this observation is general.

Barton has shown that in cyclic systems where only endocyclic elimination is possible, elimination follows the Saytzeff rule. His rationale for this observation is that there is a decreased activation energy in the series $-C-H > >C-H > \geq C-H$.¹² However, this is an oversimplification of the facts, but until more data are forthcoming, no definite statements can be made except that, empirically, thermal elimination in cyclic systems where only endocyclic elimination is possible goes according to the Saytzeff rule.

Bailey has shown that pyrolysis of 1-methylcyclohexyl acetate results in the removal of a hydrogen atom attached to the exocyclic carbon atom producing methylenecyclohexane.²⁴ This observation has been further confirmed by the synthesis of cyclolavandulol acetate (II) by Brenner and Schinz:²⁷



Bailey has concluded that these examples represent a contradiction of Barton's rule of preference of tertiary over primary hydrogen atoms,²⁴ but it must be pointed out that in all of Barton's examples, no hydrogen atoms attached to exocyclic carbon atoms were available for elimination,¹² and thus until further data are forthcoming, Barton's empirical rule of elimination according to the Saytzeff rule is still valid for cyclic systems where only endocyclic elimination is possible.

Cram has shown that the Cope transformation, the pyrolysis of amine oxides, belongs to the above family of pyrolytic elimination reactions which assume a predominately cis steric course. His results indicate that the directional course of this reaction is more specific than that observed in the pyrolysis of the corresponding xanthates.²⁸

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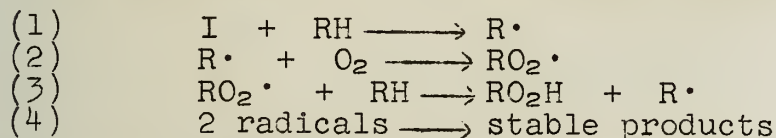
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STUDIES OF FREE RADICALS IN THE REACTION OF MOLECULAR OXYGEN WITH HYDROCARBONS

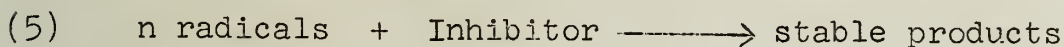
Reported by J. W. Crump

February 18, 1955

Introduction. Certain olefins and alkyl benzenes react with molecular oxygen under mild conditions to form hydroperoxides. Thus, the following oxidations all proceed in nearly quantitative yield at temperatures below 100°: cyclohexene to cyclohexene hydroperoxide^{1,2}, tetralin to tetralin hydroperoxide³, and ethyl linoleate (a 1:4-diene) to ethyl linoleate hydroperoxide (a 1:3-diene).⁴ The mechanism of this oxidation has been elucidated in detail^{5,6,7} and proceeds according to the generalized scheme (1)-(4).



In these studies, the initiation step (1) involves 2-cyano-2-propyl radicals (I) from the decomposition of AIBN. (azo-bis-isobutyronitrile). In the presence of an inhibitor, the termination step (4) may be replaced by equation (5).⁸

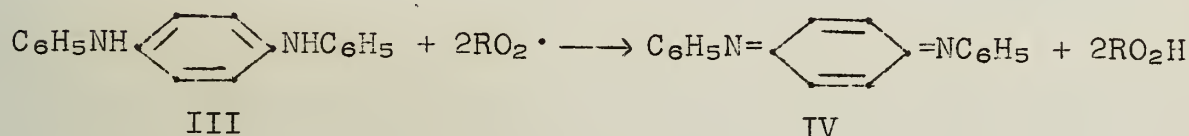
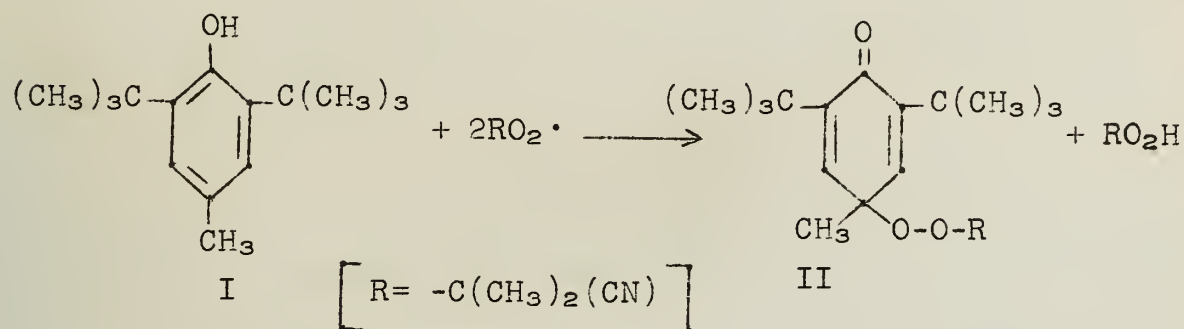


The study of the rates and products of the inhibition reaction has provided valuable information concerning the reactions of hydroperoxide radicals with phenols and amines and also information about the mechanism of decomposition of AIBN.

Behavior of 2-cyano-2-propyl radicals formed in AIBN decomposition. Although AIBN decomposes to give a quantitative yield of nitrogen, it has been shown that not all of the 2-cyano-2-propyl radicals can be captured, even by very reactive substances. Hammond and co-workers⁹ have succeeded in measuring quantitatively the efficiency of AIBN, i.e. the fraction of the total possible number of 2-cyano-2-propyl radicals which are available for reaction with iodine, mercaptans, etc. The values obtained for the efficiency depend upon the solvent used and range from 0.44 in carbon tetrachloride to 0.74 in nitromethane. This suggests that the radicals, which are formed from AIBN in pairs, may either react with each other directly, or separate into two distinct radicals in a diffusion-controlled reaction.

Reaction of 2-cyano-2-propyl radicals with chloranil. When decomposed in the presence of chloranil in chlorobenzene solution, AIBN gives the mono- and di-2-cyano-2-propyl ethers in 4 and 30% yields, respectively.¹⁰ However, if the decomposition is effected in toluene solution¹¹ the corresponding monobenzyl ether is obtained in addition to the above products. The fact that no mixed ether is formed indicates that the intermediate in the toluene reaction is probably not the p-benzyloxy-tetrachloro-phenoxy radical, since its rates of reaction with cyanopropyl radical as compared with toluene would be expected to be similar to those of the p-(2-cyano-2-propyl)-tetrachlorophenoxy radical.

Oxidation of cumene and tetralin initiated by AIBN. The effects of various inhibitors (anti-oxidants) on the oxidation of cumene and tetralin initiated by AIBN were studied.⁸ In the following two cases, the products formed from the inhibitor were isolated, and it was found that each inhibitor molecule had reacted with two radicals.



II was isolated in 50% yield and IV was determined spectrophotometrically to have been formed in 90-95% yield. With strong inhibitors, such as I and III, the hydrocarbon oxidation is completely suppressed for a period of time proportional to the initial concentration of the inhibitor (provided the inhibitor concentration is small compared to that of the initiator). By comparing the times of inhibition by other inhibitors with I and III, a stoichiometric factor, *n*, was calculated for each inhibitor studied (Table I). (Here *n* is the number of radicals removed from reaction by each molecule of inhibitor; see equation (5).)

Table I

Inhibitor	<i>n</i>	Inhibitor	<i>n</i>
2,6-di- <i>t</i> -butyl- <i>p</i> -cresol	2.0	<i>o</i> - and <i>p</i> -cresol	2.2
N-methylaniline	2.0	phenol	2.0
diphenylpicrylhydrazyl	1.98	diphenylamine	2.8

In the presence of weak inhibitors, hydrocarbon oxidation occurs at a slow, but measurable rate. With both N-methylaniline and phenol, it was found that the termination step is termolecular, that is involves the reaction of two radicals and an inhibitor molecule.¹²

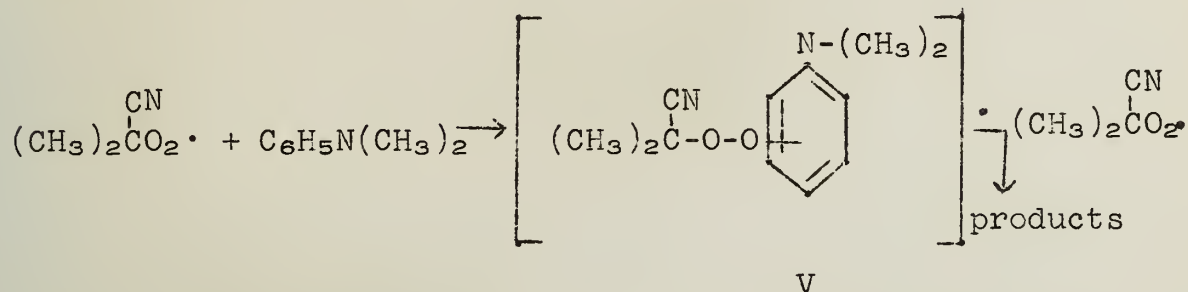
Mechanism of reaction of alkylperoxy radicals with phenols and aromatic amines. It has generally been assumed^{13,14} that the initial step in the inhibition of oxidation is the abstraction of hydrogen from the inhibitor by an alkylperoxy radical. However, Hammond et al. have shown that this is not always the case.^{12,14} Their most pertinent observations are:

- 1) N-deuterated diphenylamine and N-methylaniline show exactly the same inhibitory properties as the undeuterated compounds;
- 2) the activity of inhibitors cannot be correlated with the stability of the radicals formed by removal of hydrogen;

3) N,N-dimethylaniline and N,N,N',N'tetramethyl-p-phenylenediamine show inhibitory properties.

Thus, there must either be some alternative mechanism to hydrogen abstraction, or a third, general mechanism.

In order to explain these results, a mechanism has been suggested^{12,14} which involves the formation of a complex, V, between the radical species and the aromatic inhibitor. The following reaction sequence gives the required kinetic result, provided that the equilibrium constant for its formation is very small.



Such an intermediate could also easily explain the formation of only the monobenzyl ether of tetrachlorohydroquinone.¹¹ Similar intermediates have been proposed to account for the stereospecific addition of hydrogen bromide to 1-bromocyclohexene¹⁵, the anti-knock and anti-oxidant properties of aromatic compounds^{16,17}, and the discoloration of N,N-dimethylaniline on exposure to air.¹⁸

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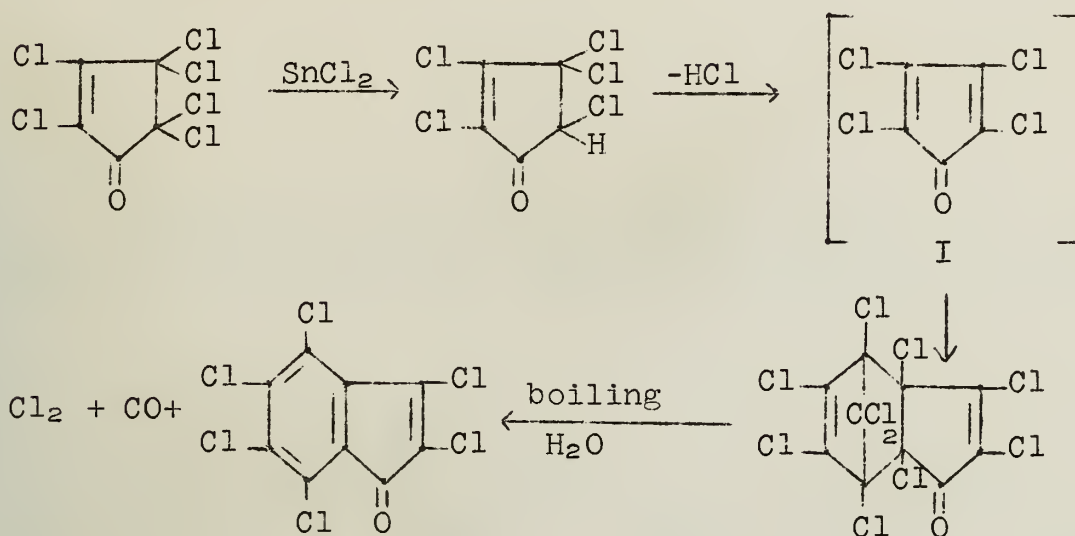
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HALOGENATED CYCLOPENTADIENES IN THE DIELS-ALDER REACTION

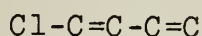
Reported by John F. Zack, Jr.

February 18, 1955

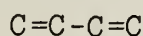
Probably the first Diels-Alder type reaction involved a halogenated cyclopentadiene^{1,2}:



Work done in the acyclic series by Coffmann and Carothers³ led Norton⁴ to the generalization that dienes having structures II or III would not add dienophiles.

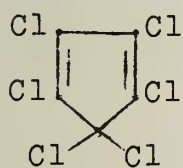


II

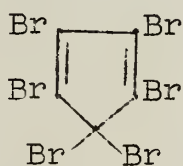


III

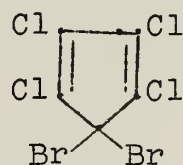
This generalization does not hold for the cyclic derivatives, however, for it was found that IV would react with a variety of dienophiles to give Diels-Alder adducts in satisfactory yields⁵.



IV

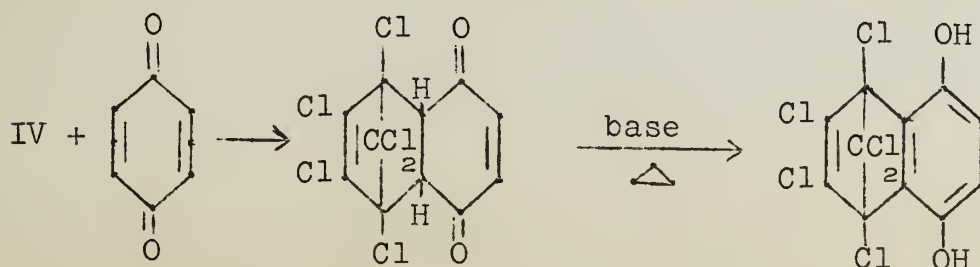


V

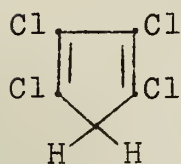


VI

A patent⁶ was issued which covered the reactions of IV, V, and VI with various quinones. These adducts could be isomerized by heating in base to give hydroquinones⁷.



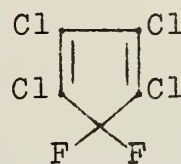
McBee^{8,9,10} prepared VII, VIII and IX and found that they all react in good yields with various dienophiles.



VII

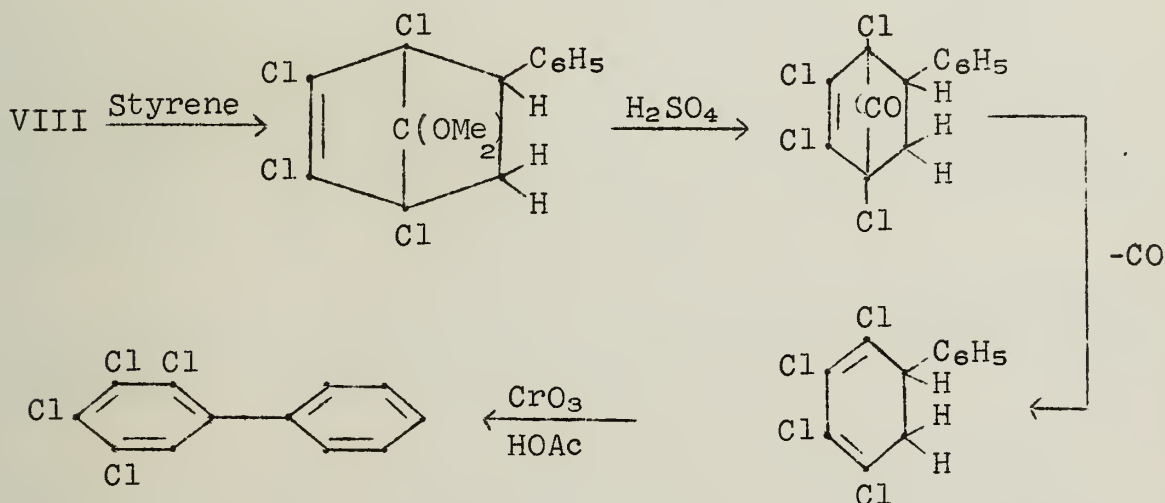


VIII

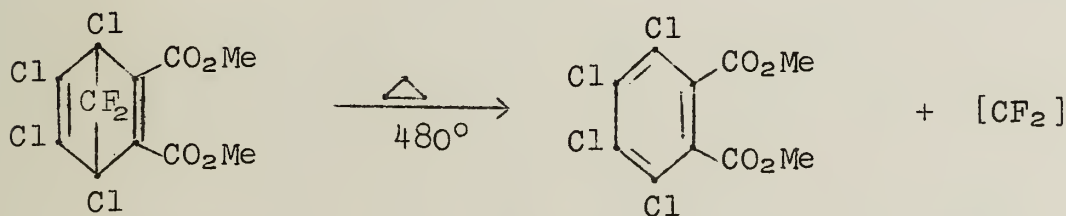


IX

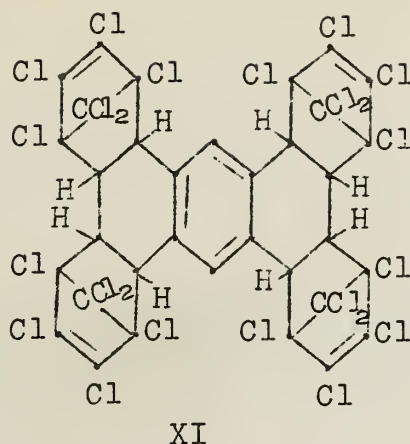
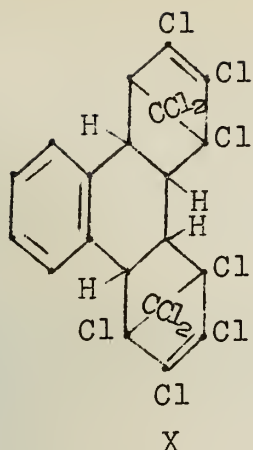
The adducts of VIII are of interest because they permit the synthesis of aromatic compounds by hydrolysis of the ketal and subsequent loss of carbon monoxide on heating⁹.



The adduct of IX with dimethyl acetylene dicarboxylate upon heating to 480° loses the elements of CF₂ instead of dissociating into the diene and dienophile¹⁰. The authors explain this on the basis of the high heat of formation of this adduct.



Danish¹¹ has found that IV will react as a diene with naphthalene and anthracene. This is the first reported reaction in which an aromatic double bond has reacted as a dienophile. The adducts formed are X and XI.



Substituents can be introduced into the aromatic rings of X and the resulting adduct will dissociate on heating in excellent yields into IV and a substituted naphthalene. Substitution occurs first in the 2-position. A second substituent will enter the 3-position. Although the 1- and 4-positions appear to be somewhat hindered, it is possible to prepare 1,2,3,4-tetrachloronaphthalene. Other naphthalene derivatives which were made in this manner are 2-nitronaphthalene (97%), 2-bromonaphthalene (79%) and 2,3-dibromonaphthalene (80%). (Yields are based on X).

Alternative structures can be written for the adducts of naphthalene and anthracene with IV on the assumption that the aromatic compounds had acted as dienes. Danish presents evidence that IX and X are correct.

It is of interest to note that I, VII and IX will dimerize but IV, V, VI and VII do not. 1,2,3,4,5-pentachloropentadiene will also dimerize. Apparently a very large group above and below the plane of the ring prevents the compounds from reacting as a dienophile, and dimerization will not take place.

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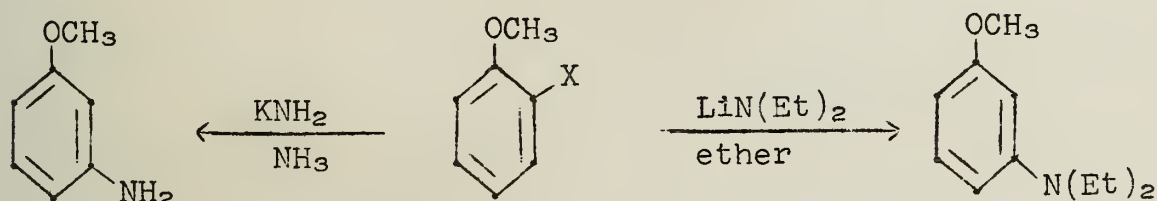
A MECHANISM FOR THE AMINATION OF ARYL HALIDES

Reported by R. L. Pedrotti

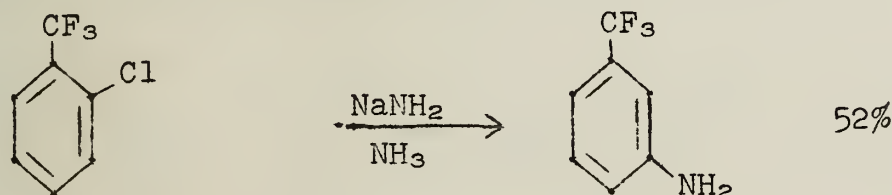
February 25, 1955

Although rearrangements in the amination of non-activated aryl halides with alkali metal amides have been known for many years, no satisfactory explanation had been published until recently. The mechanism recently proposed by Roberts, Simmons, Carlsmith, and Vaughan will be the subject of this seminar.^{1,3}

Phenyl halides react with either potassium amide in liquid ammonia or with lithium diethylamide in ether to give, respectively, aniline and diethylaniline. *o*-Haloanisoles react with these reagents as indicated:²



It was observed by Benkeser and Severson that the same rearrangement occurs when the halogen is ortho to a strong meta-directing group.⁴



m-Chlorotrifluoromethylbenzene also gives the same product in 35% yield.

α -Halonaphthalenes(Cl, Br, I) react with potassium amide to give β -naphthylamine in 43-45% yield and α -naphthylamine in 2-3% yield.^{5,6} Similarly α -halonaphthalenes(Cl, Br) give β -diethylaminonaphthalene on treatment with lithium diethylamide as the major product.

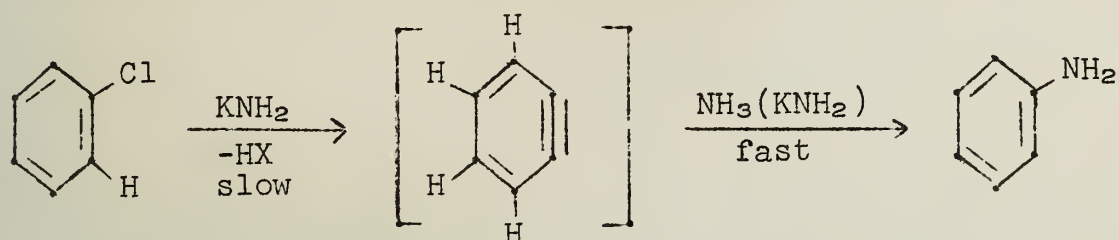
In contrast the normal β -substituted products are obtained from the β -halonaphthalenes. α -Fluoronaphthalene on treatment with potassium amide gives the normal product and with lithium diethylamide gives 20% of normal product and 40% rearranged product.⁵ Both normal and rearranged products are obtained from *p*-bromoanisole, *p*-chlorotoluene, and halodibenzofurans.^{8,9,10}

From the experiments cited above and from other related experiments the following facts were accumulated:¹

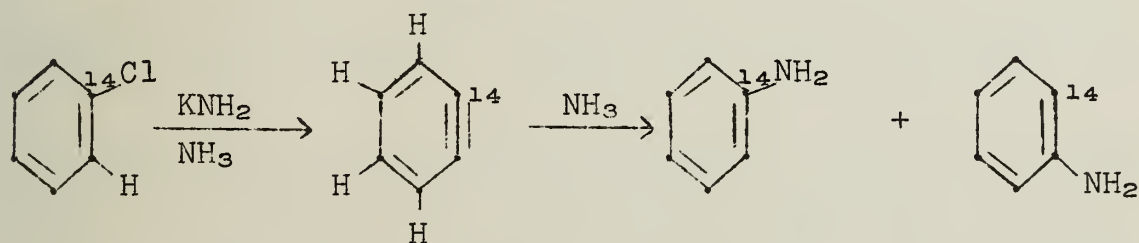
- (1) The reactions are very rapid, even with chlorobenzene, in liquid ammonia at -33°C .
- (2) The entering amino group has never been found further than one carbon away from the position occupied by the leaving halogen.

- (3) The starting halides and resulting anilines are not isomerized under the reaction conditions.
- (4) A strong base is required.
- (5) No reaction occurs in the benzene series with halides (bromomesitylene, bromodurene and 2-bromo-3-methylanisole) where a hydrogen is not attached to the position adjacent to that occupied by the leaving halogen.

These facts led Roberts and coworkers to postulate an elimination-addition mechanism involving at least a transitory existence of an electrically neutral "benzyne" intermediate.



The symmetrical "benzyne" intermediate suggests that attack could occur at either end of the "triple-bond". This was found to be true, for chlorobenzene-1- C^{14} gave almost exactly equal amounts of aniline-1- C^{14} and aniline-2- C^{14} .¹

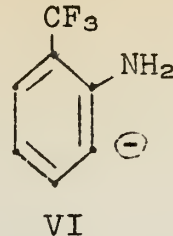
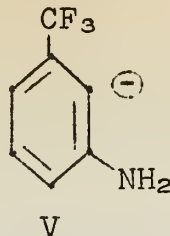
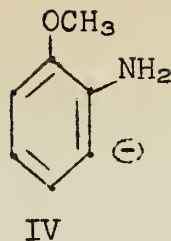
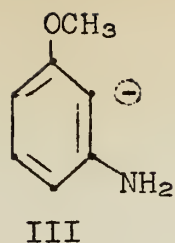


The fact that no reaction occurs when an α -hydrogen is absent and that chlorobenzene-2-D reacts more slowly than ordinary chlorobenzene is added evidence that the breaking of the α -hydrogen bond is the rate-determining step.²

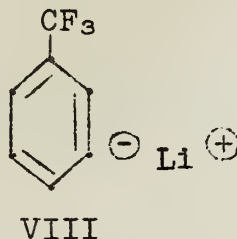
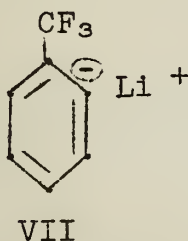
The benzyne type intermediate for *o*-haloanisole and *o*-halotrifluoromethylbenzene are represented by structures I and II.



It is evident that the intermediate is no longer symmetrical and addition can occur only at the meta-position if a rearranged product is to be obtained.



The results of metalation studies provide evidence that structures III and V are preferable to IV and VI. Roberts and Curtin have shown that in the metalation of benzonitrile with *n*-butyl lithium the ortho isomer VII is produced in a ratio of five to one over the meta isomer VIII.¹¹



A metalation experiment was carried out with anisole. After carbonation a 40% yield of almost pure *o*-anisic acid was isolated.¹¹ It had been shown previously that anisole, phenetole and *p*-bromoanisole react with alkyllithium compounds to give principally products in which lithium had entered a position ortho to the methoxyl group.¹²

These examples indicate that in the transition state a negative charge ortho to the methoxyl or trifluoromethyl is better tolerated and thus justify structures III and V.

The results of a study of absorption spectra of acetylene have recently been reported by Ingold and coworkers. They claim experimental evidence for a trans-bent excited state of acetylene. They also propose that a cis-bent state exists. They suggest that the "triple-bond" of the benzyne intermediate should be very much like the cis-bent state of acetylene.

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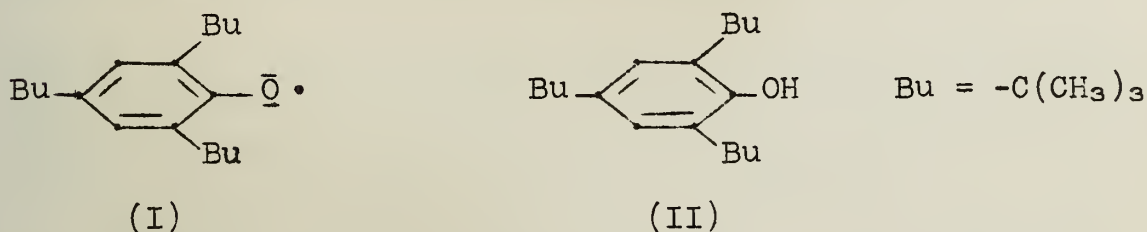
BEHAVIOR OF STABLE FREE RADICALS

Reported by R. M. Nowak

February 25, 1955

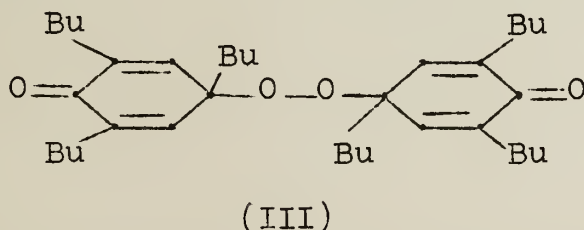
The discovery of the triphenylmethyl radical and its reactions¹⁻¹⁵ initiated the preparation and study of relatively stable free radicals. In addition to analogs of hexaphenylethane, studies were carried out on aromatic compounds such as tetraphenylhydrazine¹⁶ which dissociate into divalent nitrogen free radicals. The diphenyl amino radical and its analogs were found to undergo many of the same reactions as the triphenylmethyl radical.¹⁷⁻¹⁸

Recently a stable univalent oxygen free radical, 2,4,6-tri-tert-butyl phenoxyl (I), has been synthesized by the oxidation of the tri-tert-butyl phenol (II).¹⁹⁻²⁰ When (II), dissolved in a non-ionic solvent, is dehydrogenated



with active lead oxide, silver oxide, or potassium ferricyanide, a deep blue solution is obtained. Filtration and evaporation to dryness under reduced pressure yields a dark blue air sensitive crystalline solid whose structure has been designated as (I).¹⁹ This phenoxyl radical does not couple as do substituted p-methyl phenols,²¹ but is stable for a long time in the absence of air.

The blue radical (I) is extremely air sensitive in solution as well as in solid form. The rapid oxygen uptake of the radical is virtually quantitative. From the solution a yellow crystalline solid is obtained whose analyses, molecular weight and infrared absorption check for bis-[1,3,5-tri-tert-butyl cyclohexadienone-4]-1-peroxide (III). An ortho-ortho or ortho-para possibility also exists.

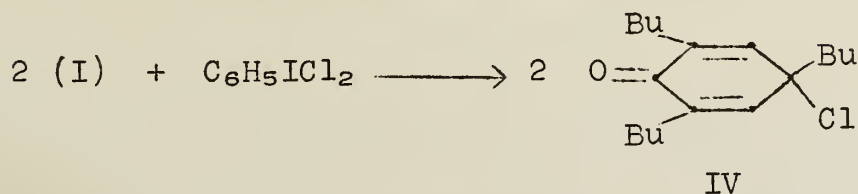


This peroxide like the free radical (I) is light and air sensitive.

Catalytic hydrogenation of (I) with platinum in acetic acid proceeds quickly to give a colorless solution from which the original phenol can be quantitatively isolated. The radical can be determined quantitatively by reduction using either hydrazobenzene or sodium iodide in acetic acid.

Chlorination of the radical can be accomplished by either

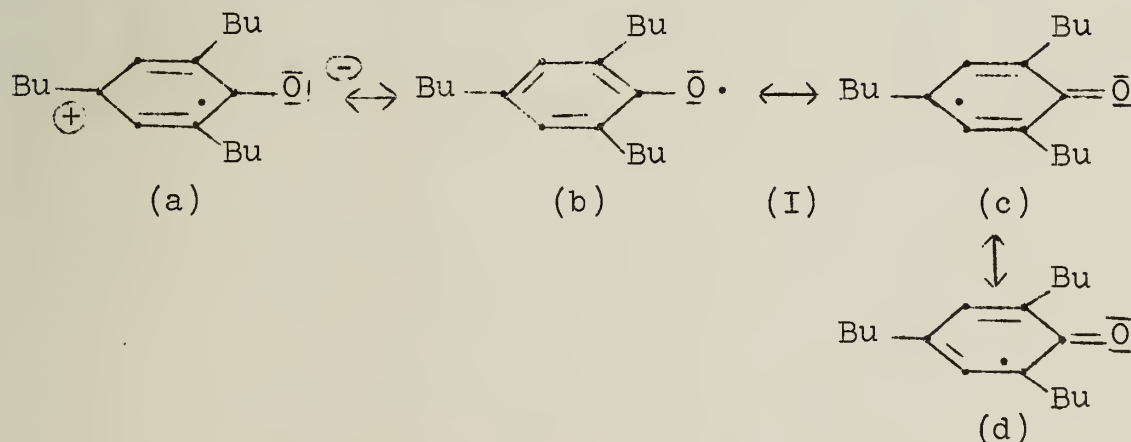
the action of phenyliodosochloride on the free radical or the action of chlorine in acetic acid on the phenol. A green crystalline solid is obtained whose elementary



analyses; molecular weight, and infrared absorption spectrum are consistent with compound (IV). The chlorine atom can easily be removed by warming with a metal such as copper or sodium to give the free radical. This is a more convenient method for preparing the univalent oxygen radical than is the oxidation of the phenol.

The rate of reduction of radical (I) with phenol and substituted phenols depends upon the acidity of these phenols. The more acidic the phenol; the slower is the reaction. Picric acid and 3-nitrophenol decolorize the radical solution slowly while the action of phenol is immediate.

Magnetic susceptibility measurements confirm the free radical nature of (I). Infrared studies also give good indications of the structure. Discrete absorption bands at 6.0 μ and 6.2 μ in structure (III) and (IV) correspond to a quinoid structure. In (I) there is only a single absorption band between 6.0-6.2 μ . However, a new band appears at 6.4 μ , which is characteristic of a carboxyl or nitro group. Very probably this band can be attributed to >C=O^\ominus or >C=O^\bullet . Taking into account all the data the following resonance structures have been postulated. The



6.4 μ band is attributed to either structure (a) or (b); the data apparently cannot be used to differentiate between the two forms. As a solution of (I) is diluted the absorption at 6.4 μ is greatly reduced as that at 6.0-6.2 μ increases. This is probably based upon a shift from the (a) and (b) structures to (c) and (d) as the radical concentration becomes more dilute. A 6.4 μ band cannot definitely be

attributed to $\equiv\text{C}-\bar{\text{O}}\cdot$ or $\text{>C}-\bar{\text{O}}\ominus$ since this is the first example of this absorption reported.

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THE EFFECT OF AN ANGULAR METHYL GROUP ON THE STABILITY OF FUSED RING SYSTEMS

Reported by Ronald R. Sauers

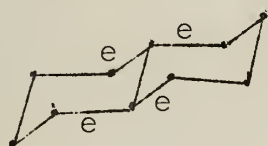
March 4, 1955

The relative stabilities of cis and trans fused ring systems seem to depend mainly on the size of the rings involved. Work by Huckel^{1,2} and Linstead³ has demonstrated that at equilibrium the trans form was favored in all systems studied which contained two fused 6-membered rings (including heterocyclic oxygen). In systems containing either two fused 5-membered rings or a 5-membered ring fused to a 6-membered ring, (including heterocyclic oxygen and nitrogen) the cis form predominated at equilibrium.

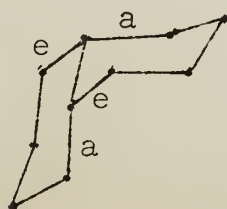
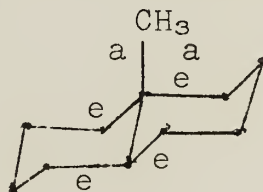
These generalizations have been rather liberally applied in studies of the stereochemistry of steroids.⁴ It should be noted, however, that whereas many of the basic generalizations were made on rather simple bicyclic systems, the steroid studies were made on compounds containing angular methyl groups (along with other complicating factors). The effect of the angular methyl group on the relative stabilities of fused ring systems will be discussed here.

Bachmann and Dreiding⁵ carried out the first set of experiments to study the effect of angular methyl on the above generalizations. These authors showed that systems containing angular methyl in the hydrindane skeleton were more stable in the cis-form (over palladium at 250-300°).

The results with systems containing angular methyl and two fused 6-membered rings are not yet conclusive. The methods of conformational analysis⁶ lead one to predict that trans-decalin would be more stable than cis-decalin. This conclusion is arrived at by comparing the number of axial and equatorial carbon-carbon bonds in the two systems. It is seen that trans-decalin (Figure I) has four equatorial C-C bonds. In cis-decalin, however, only two C-C bonds may be equatorial; the other two must be axial. The presence of angular methyl changes these ratios, however. The cis form of 9-methyldecalin has three equatorial and three axial C-C bonds as compared to the trans form which now has four equatorial and two axial C-C bonds (Figure II). The energy differences between the alkylated epimers must be less than the energy differences between the unsubstituted decalins.



TRANS



CIS

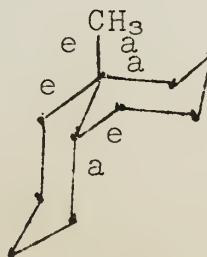


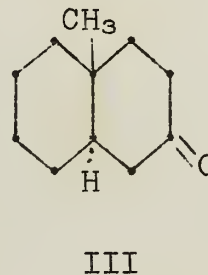
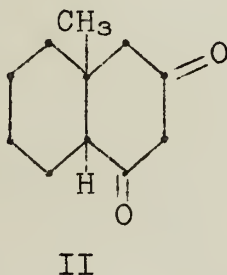
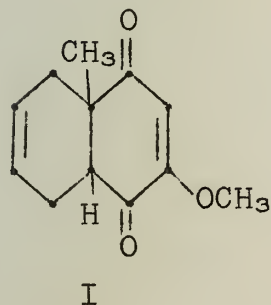
Figure I

Figure II

A more quantitative estimate of the decrease in the relative stabilities of 9-methyldecalins was made by Turner⁷. Based on the finding by Pitzer⁸ that the skew form of n-butane is 0.8 kcal/mole less stable than the staggered form, Turner predicted that the energy difference between cis and trans decalin is decreased from 2.4 to 0.8 kcal/mole upon introduction of angular methyl. Turner assumed, however, that a methyl and a methylene group had the same energy of steric interaction. If a methyl group is assumed to have a slightly greater steric effect than methylene, the relative stabilities would be diminished further (or even reversed). In spite of the fact that cis-9-methyldecalin has one more overall skew interaction than the trans epimer, the latter has four interactions involving skew methyl while the former has only two such interactions.

The experimental evidence is likewise inconclusive. Hibbit and Linstead⁹ claimed to have isomerized cis-9-methyldecalin to the trans epimer by means of AlCl_3 . Subsequent work by Dauben et al¹⁰ has shown that Linstead's "cis" isomer was actually mainly trans, and that the product of isomerization was probably a mixture of products containing "deep-seated" skeletal rearrangement products (along with the desired epimers).

Woodward¹¹ and Linstead¹² state that the cis compounds I and II possess unusual stability. Dreiding and Tomasewski¹³, on the other hand, report that III is stable in the presence of Raney nickel.



A recent study by Bachmann and coworkers¹⁴ indicates that the introduction of angular methyl into decahydroisoquinoline-1,3-diones reverses the order of stability (over palladium at ca. 250°). See Figure II.

Composition at Equilibrium

	% <u>CIS</u> 32	% <u>TRANS</u> 68
	60	40
	71	29

Figure II

Although this study was carried out on heterocyclic compounds, there is ample reason to believe that it applies to isocyclic systems. The ΔH of isomerization of the decahydroisoquinolinediones, for example, is about the same as that reported for the decalins. Likewise, conformational analysis seems to apply equally well to either type of system.^{15,18}

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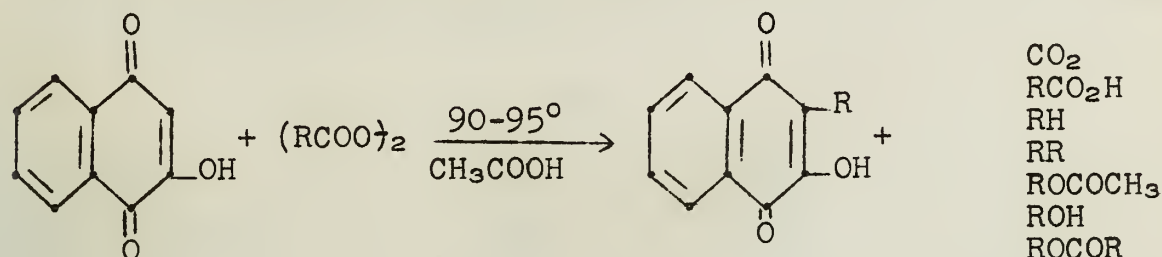
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FREE RADICAL AROMATIC SUBSTITUTION

Reported by A. T. Tweedie

March 4, 1955

Free radical aromatic substitution reactions give random orientation and lead to large numbers of products and tars. Good results have been obtained in specific instances, however. Fieser and co-workers obtained many derivatives of 2-hydroxy-1,4-naphthoquinone in adequate yields by reaction of this substance with various diacyl peroxides.¹



In this case there is only one position likely to be attacked, so the problem of isomer formation is avoided. This discussion deals primarily with the effect of substituents on the benzene ring in phenyl radical substitution reactions.

A complete knowledge of the influence of a substituent on aromatic substitution requires a knowledge of its directing influence and overall activating or deactivating effect. Since the formation of the attacking radical has been found to be the rate determining step⁴, the competitive method of determining rate constants rather than direct measurement must be used in studying free radical substitutions. In this method an equi-molar mixture of two compounds is allowed to react in a homogeneous solution with a small quantity of the substituting agent. The ratio of the rate constants is equal to the relative amounts of the products formed, provided the reactions are of the same kinetic order. Using nitrobenzene as the reference solvent and the thermal decomposition of benzoyl peroxide as a source of phenyl radicals, Hey and associates determined relative rate constants for several substituted benzenes. They were able to isolate quantitatively the biphenyl fraction by distillation. The nitrophenyl component in the biphenyl fraction was determined by titration with titanous chloride. The rate constant relative to benzene is expressed as $\text{PhX}/\text{PhH} K$, where PhX is the substituted benzene and PhH is benzene.

Of all the substances studied thus far only the *t*-butylbenzenes deactivate the ring. This effect is attributed to steric hindrance of the ortho positions, which in effect reduces the opportunity for reaction. The fact that widely varying groups all behave more or less similarly shows that electrostatic effects have little influence.

The directing influence of substituents on the benzene ring has been studied by spectroscopic analysis of the mixture of isomers formed.^{4,5,8,9} Using the rate constant, $\text{PhX}/\text{PhH} K$, and the percentages of isomers formed, partial rate factors may be calculated.⁴ These are the rates of attack on the ortho, meta and para positions of a substituted benzene in

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ORIGINAL ARTICLES

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terms of the rate of attack on any one position of benzene. The partial rate factor of benzene is unity by definition. The following equation expresses the relation between the rate constant and the partial rate factors for a mono-substituted benzene.

$$\text{PhX/PhH } K = \frac{1}{6} (2F_o + 2F_m + F_p)$$

Table one shows partial rate factors based on percentages of isomers obtained, when single compounds were allowed to react with phenyl radicals.^{4,5,8,9}

Table One

<u>Solvent</u>	<u>F_o</u>	<u>F_m</u>	<u>F_p</u>
Fluorobenzene	2.20	1.25	1.20
Chlorobenzene	2.7	1.03	1.2
Bromobenzene	2.55	1.73	1.83
Iodobenzene	2.79	1.70	1.84
Nitrobenzene	6.9	1.2	7.9
Pyridine	1.91	0.86	1.01
Naphthalene	29.9	6.0	---
Biphenyl	2.9	1.4	3.4
<u>t</u> -butylbenzene	0.63	1.28	1.41
<u>p</u> -di- <u>t</u> -butylbenzene	0.93	0.93	---

Most of the compounds shown in Table one are ortho-para directing and mildly activating in all positions. The fact that the meta and para positions in t-butylbenzene show activation may mean the t-butyl group is intrinsically activating.

Dannley and coworkers using pyridine as a reference solvent have substantiated to a large degree the work outlined above.^{10,11,12} They have also done some interesting work involving change of the attacking free radical.¹² In benzotrichloride both the substituent and the ring may undergo free radical attack. If a series of substituted phenyl radicals react with this substance, a change in the substituent on the radical may vary the ratio of nuclear to side chain attack and/or alter the orientation of the substitution on the nucleus. Table two shows the results of this work.

Table Two

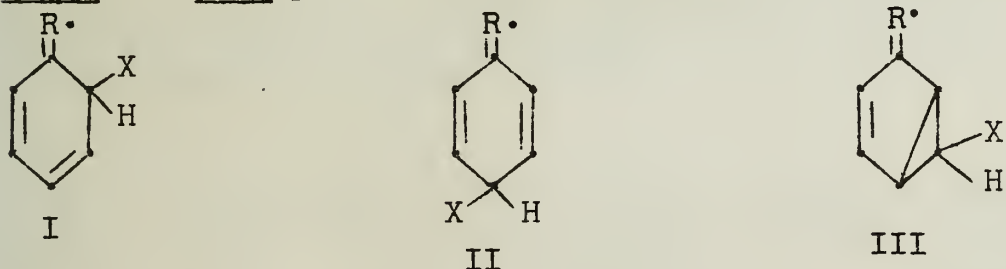
<u>Radical</u>	<u>Solvent</u>	Ratio of side chain to nuclear attack	Isomers formed		
			<u>ortho</u>	<u>meta</u>	<u>para</u>
phenyl	benzotrichloride	2.7	0	60%	40%
<u>p</u> -chlorophenyl	"	0.46	0	83	17
<u>p</u> -nitrophenyl	"	0	0	100	0

It is evident that aryl free radicals are influenced by their substituents. Dannley states that the chlorine atom which must be released by the trichloromethyl group in side chain attack is itself primarily an electron acceptor. Consequently, it should be least susceptible to attack by the similarly electron seeking nitrophenyl radical and most susceptible to reaction with the phenyl radical. When

reaction with the side chain is not preferred, nuclear substitution occurs.

Dannley further states that the complete lack of ortho substitution in benzotrichloride may be explained by steric hindrance. The increase in yield of meta isomer on passing from phenyl to chlorophenyl to the strongly electron seeking nitrophenyl radical is logical on the basis that the meta position of benzotrihalides is known from ionic substitution studies to have a higher electron density than the para position. In fact, it seems likely that substitution in aromatic nuclei by radicals highly deficient in electrons (e.g. nitrophenyl) may follow the rules for orientation established for ionic nucleophilic reagents. Conversely, radicals rich in electrons (e.g. p-anisyl) may obey the rules established for electrophilic substitution.

Hey, Nechvatal and Robinson propose the following resonance forms of the transition state to show how a substituent may stabilize the transition state and to account for why the ortho and para positions are favored.



R• is any substituent and X• is the entering free radical. I and II are considered more stable than III.

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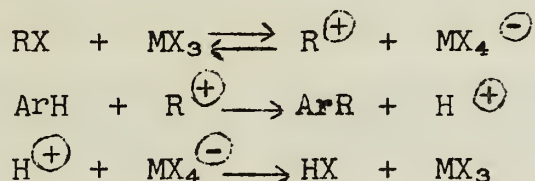
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THE STEREOCHEMISTRY OF AROMATIC ALKYLATIONS

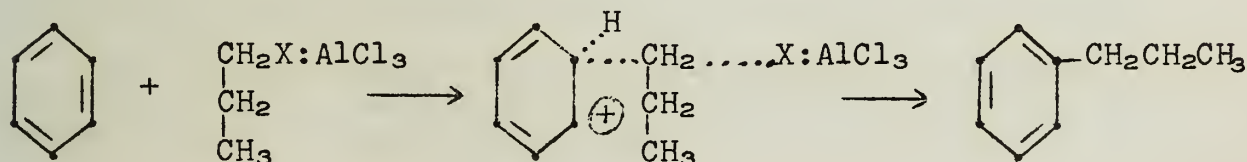
Reported by Ralph Farrar

March 11, 1955

A generally accepted mechanism for Friedel-Crafts substitution is an ionic process involving production of a carbonium ion.¹



Most substitutions are explained very well by this mechanism, but there are some which do not fit this picture. Among these are the high yields of n-propylbenzene obtained in the alkylation of benzene with n-propyl chloride and the sole formation of the n-propyl isomer in the alkylation of benzene with n-propyl alcohol and aluminum chloride. Another example is the formation of neopentyl benzene in the alkylation of benzene with neopentyl alcohol and aluminum chloride.² Brown and Grayson³ and Schmerling⁴ suggest that a displacement reaction accounts for these results.



X = OH , Cl

They³ found that in certain cases (primary and sometimes secondary halides and alcohols) the alkylation does indeed have third order kinetics. Thus if the alkylating agent is an optically active secondary halide or alcohol a product having some optical activity rather than a completely racemized one should be formed.

Experiments were conducted in which benzene was alkylated with optically active sec-butyl alcohol^{5,6} and sec-butyl methyl ether⁷, but the product was extensively racemized.

C-alkylation occurring along with O-alkylation in the Claisen preparation of alkyl phenyl ethers has been observed to give optically active nuclearily alkylated phenols⁸, but the extent of optical purity and the relative configurations of the starting materials and products were not ascertained. Hart and Eleuterio⁹ studied this reaction using phenol, p-cresol, and 2,6-xylenol as the phenols and optically active α-phenethyl chloride as the alkylating agent in all cases. The relative configurations of the starting material and product were established. Phenol and p-cresol reacted with inversion of configuration and maximum retention of optical purity on the order of 64%. With 2,6-xylenol the extent of racemization was somewhat higher.

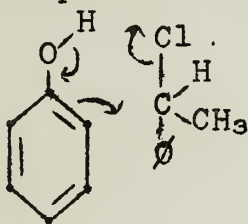
The thermal rearrangement of alkyl aryl ethers is known to produce an alkylated phenol^{10,11,12}. Hart and Eleuterio¹³ investigated this reaction using the optically active α -phenethyl ethers of the three phenols mentioned above. They established the configurations of the ethers and then heated each ether without a solvent at 200°C for about five hours. Yields of the alkylated phenols were 25-35%.

It was established that the rearrangement proceeded with retention of configuration. No matter whether the product was ortho or para the extent of retention was about 20% (a minimum value).

The catalyzed rearrangement of the ethers was also studied¹⁴ and shown to involve retention. The reaction proceeded with high retention of optical purity.

Hart, Spliethoff and Eleuterio¹⁵ recently studied the alkylation of phenols with optically active α -phenethyl chloride, a reaction which proceeds without a catalyst. The phenols employed were the three listed above and *p*-chlorophenol. 2,6-Xylenol reacted with inversion while the other phenols reacted with retention of configuration. All of the products were extensively racemized. Note that 2,6-xylenol is the only phenol in which the ortho positions are blocked.

The authors suggest that the reaction with retention involves a cyclic mechanism in which the ortho carbon of the phenol acts as a nucleophilic site.



Thus the stereochemical result in this case is not inversion as predicted by Brown's work, but this is only because the acid catalyst and the aromatic component are a part of the same molecule.

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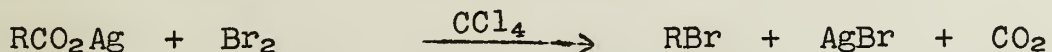
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THE DECARBOXYLATION OF SILVER SALTS WITH BROMINE

Reported by William G. DePierri, Jr.

March 11, 1955

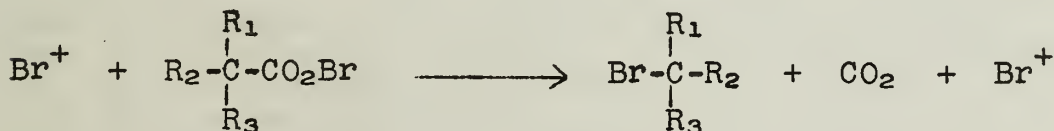
When metallic salts of carboxylic acids in solution or suspension are treated with free halogen, a reaction occurs in which a variety of products are obtained.^{1,2} If the silver salt of the acid is treated with bromine using carbon tetrachloride as the solvent, the principle reaction is usually that of decarboxylation with the formation of an alkyl bromide with one less carbon atom;³



The parent acid and the ester which would be expected by the reaction of the silver salt with the alkyl bromide are rather consistent by-products which are found in varying amounts depending upon the silver salt and the conditions of the reaction.^{4,5}

The mechanism of this reaction has been the subject of investigation for several years. Early workers concluded that the course of the reaction involved an acyl hypobromite intermediate, which decomposed with the evolution of carbon dioxide to form the alkyl bromide.⁶ Evidence for this intermediate involves the reactions of a colored complex which forms when silver butyrate is treated with bromine in cold carbon tetrachloride. The complex was found to have an oxidizing power of two equivalents per mole, and was also found to add to cyclohexene to give the ester, 2-bromocyclohexyl butyrate. Other examples of additions to a double bond by acyl hypohalites formed by the action of a halogen upon a silver carboxylate have been cited.⁷

At least two distinct mechanisms have been postulated for the reaction. Arcus and coworkers⁷ proposed essentially a rearward attack of a positive bromine upon the acyl hypohalite intermediate to displace carbon dioxide and a positive bromine with inversion of configuration. Evidence offered to support this mechanism involves the isolation of



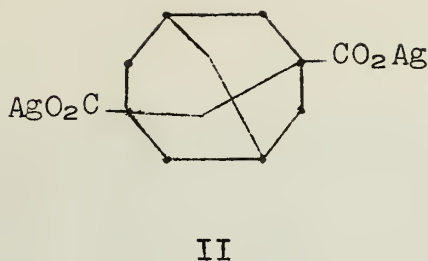
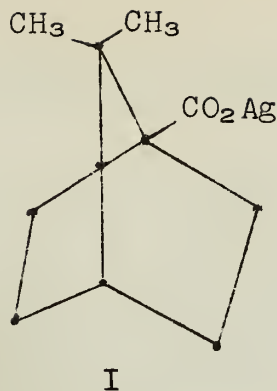
optically active products with inversion of configuration in two cases, that of silver (+)- α -phenylpropionate and silver (+)-2-ethylhexanoic acid.⁹ However, efforts to repeat the work in the first case have met with failure.¹⁰ Further evidence against this mechanism has been accumulated since silver 1-apocamphancarboxylate (I) and silver adamantane-1,3-dicarboxylate¹² (II) both undergo brominative decarboxylation. In both cases, steric considerations make a rearward attack with inversion of configuration impossible. Also, it has been shown that optically active β -phenylethyl bromide racemizes completely under the experimental conditions used by Arcus.¹³

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Price has proposed the following mechanism for the reaction.¹⁴

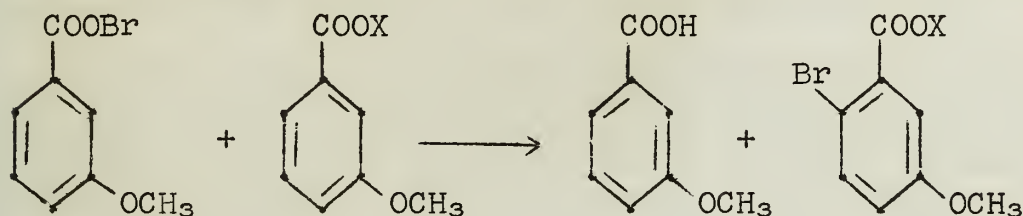
- 1) $\text{Br}_2 \longrightarrow 2\text{Br}\cdot$
- 2) $\text{RCO}_2\text{Ag} + \text{Br}\cdot \longrightarrow \text{RCO}_2\cdot + \text{AgBr}$
- 3) $\text{RCO}_2\cdot \longrightarrow \text{CO}_2 + \text{R}\cdot$
- 4) $\text{R}\cdot + \text{Br}_2 \longrightarrow \text{RBr} + \text{Br}\cdot$

Through the efforts of several workers in this field, a large body of evidence has been accumulated which tends to support such a free radical mechanism. Early workers reported that light causes an acceleration of the rate of the decarboxylation^{1,6}, an effect which is especially noticeable in the case of mercury salts. Further evidence includes the work of Dauben and Tilles¹⁵ who treated silver benzoate in boiling carbon tetrachloride with bromine. In addition to the bromobenzene which was isolated, bromotrichloromethane and chlorobenzene were also found in significant amounts. These products certainly suggest a free radical mechanism. Also bromodichloromethane has been isolated when methylene chloride was used as a solvent¹⁶ and some dibromoheptanes were obtained when silver caprylate was treated with bromine.¹⁰

The stereochemical aspects of the reaction are entirely consistent with a free radical mechanism. In the brominative decarboxylation of silver *t*-butylacetate, neopentyl bromide was the only bromide isolated. If the reaction proceeded through an intermediate carbonium ion, it would be reasonable to expect some rearrangement with the resultant formation of some *t*-amyl bromide. The reaction of silver cyclobutanecarboxylate with bromine gave primarily cyclobutyl bromide along with smaller amounts of tribromobutanes and an ester, which was assumed to be cyclobutyl cyclobutanecarboxylate.¹⁸ However, further work by Roberts and Simmons¹⁹ demonstrated that the ester was actually a mixture of cyclobutyl, cyclopropylcarbinyl and allylcarbinyl cyclobutane carboxylates. They further found that a mixture of esters of approximately the same constitution could be obtained by the reaction of cyclobutyl bromide with silver cyclobutanecarboxylate. Roberts postulates that the mixture of esters is a result of a carbonium ion intermediate in the reaction between cyclobutyl bromide and silver cyclobutanecarboxylate and not

from rearrangements which occur during the formation of cyclobutyl bromide.

It has been found that the course of the reaction in the case of aryl carboxylates is often more complex than it is in the alkyl series. Dauben and Tilles¹⁵ found that the reaction proceeds satisfactorily when the ring is substituted with electron withdrawing groups such as nitro or chloro, but gives increasingly large amounts of brominated acid as the electron density of the ring is increased. A mechanism for the bromination of aryl acids whereby the acyl hypobromite is the brominating agent was proposed.¹⁵



X H, Ag or Br

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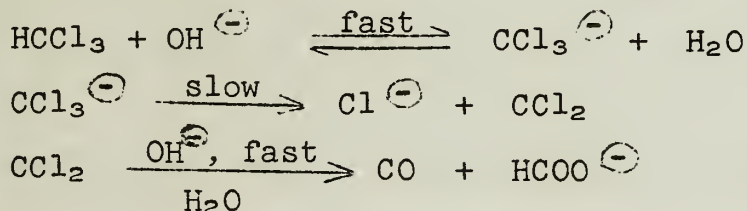
THE REACTION OF HALOFORMS WITH BASES

Reported by F. W. Wassmundt

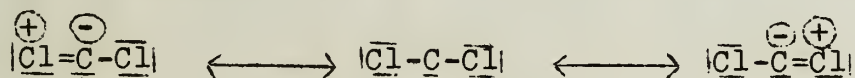
March 18, 1955

The action of aqueous alkalis upon haloforms has long been known to produce carbon monoxide and formates.^{1,2} Early investigators viewed the haloform molecule as $CX_2 \cdot HX$; treatment with a base was thought to liberate CX_2 , which was then hydrolyzed to carbon monoxide. Alkaline aqueous ethanol was observed to attack haloforms to give a small percentage of ethylene. Hermann¹ believed that the olefin was produced by dehydration of the alcohol. However, Nef³ supposed that it arose from the coupling of two CHX fragments and regarded $H CX \cdot X_2$ as another possible structure of the haloforms.

An early study⁴ of the exchange between heavy water and chloroform revealed that the chloroform rapidly interchanged its hydrogen atom with the water before decomposition; this interchange in neutral or acidic solution is far slower than in alkaline solution. Hine,⁵ employing $DCCl_3$ and base, reached the same conclusions. The rate of hydrolysis, which is subject to general base catalysis, is about 2000 times that of decomposition. The hydrogen atom of chloroform is about as reactive as the α -hydrogens of acetaldehyde or acetone. This investigator⁶ had found the reaction between alkali and chloroform to be first order with respect to each reactant; he proposed this mechanism:



Dichlorocarbene would be expected to be resonance stabilized. The principal contributing structures are probably these:



Hine⁶ suggested that reactions which involve chloroform and a base as starting materials (such as the formation of orthoformate esters from alkali metal alkoxides, the Reimer-Tiemann reaction, the formation of isonitriles from primary amines, the formation of β -chloropyridine from pyrrole) involve dichlorocarbene as an intermediate.

A recent investigation⁷ of the origin of the ethylene produced from the reaction of haloforms with alkaline aqueous ethanol has shown that the alcohol is dehydrated. Thus, the propanols yield propene; the butanols, the butenes; etc. While the method is of little synthetic value, it is noteworthy that the reaction follows the Hofmann elimination rule.

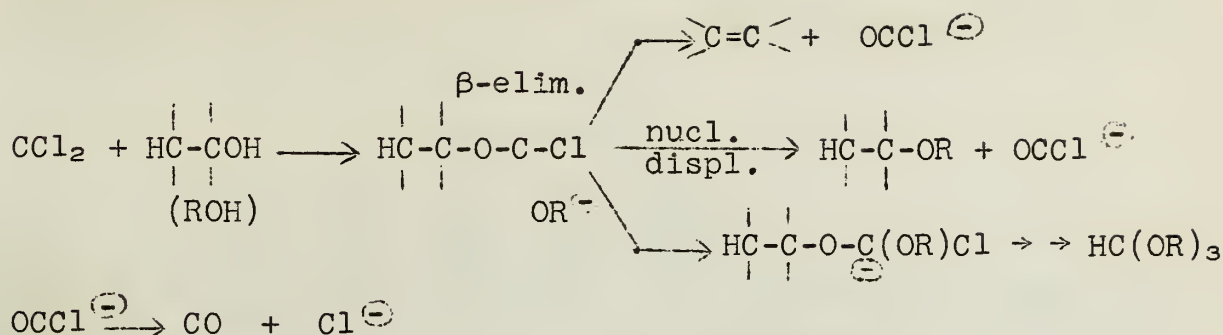
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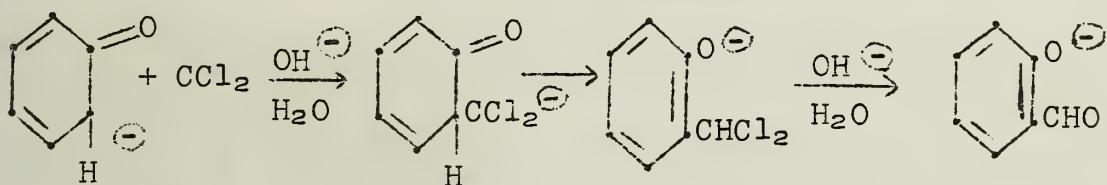
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The suggested mechanism is this:



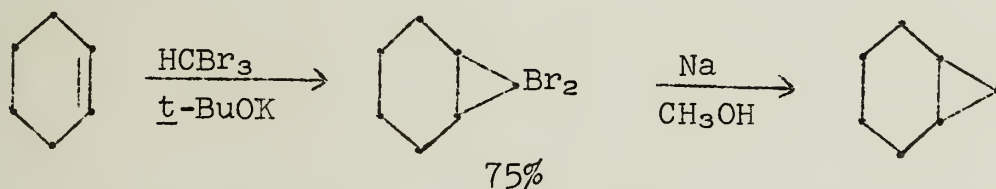
Presumably, an analogous intermediate (RNH-CCl) exists in the formation of isonitriles.

In a note which criticizes the Armstrong-Richardson mechanism⁸ for the Reimer-Tiemann synthesis, Wynberg⁹ employed dichlorocarbene as an intermediate.



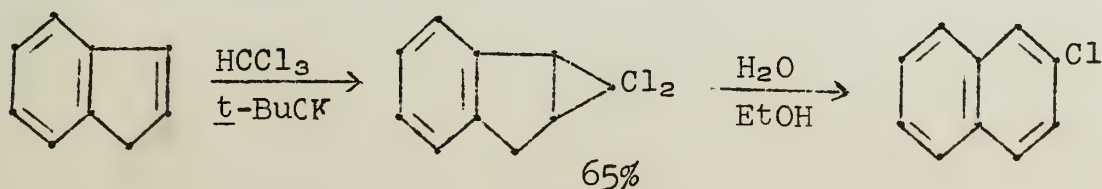
Utilization of the mechanism studies has led to several new synthetic methods. Recognition of the intermediate anion formation led Bergmann¹⁰ to obtain better yields of aryltrichloromethylcarbinols than those previously achieved.¹¹

Doering¹² has found that dichlorocarbene and dibromocarbene add readily to olefins. The synthesis of norcaradiene is an interesting example.



Failure to isolate such compounds as $\text{>C(CCl}_3\text{)CH<}$ supports the contention that it is not the CCl_3^- anion which adds to the double bond.

Parham¹³ has provided a novel synthesis for β -chloronaphthalene. Apparently, the second step is an E_1 elimination.



It is thought that ethyl diazoacetate decomposes to form carbethoxycarbene.¹⁴ The decomposition of diazomethane probably provides a CH₂ entity.^{15,16} Presumably a phenylchlorocarbene is involved in the formation of β-phenylpyridine from pyrrole, benzal chloride, and base.

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THE S-TRIAZINE RING SYSTEM

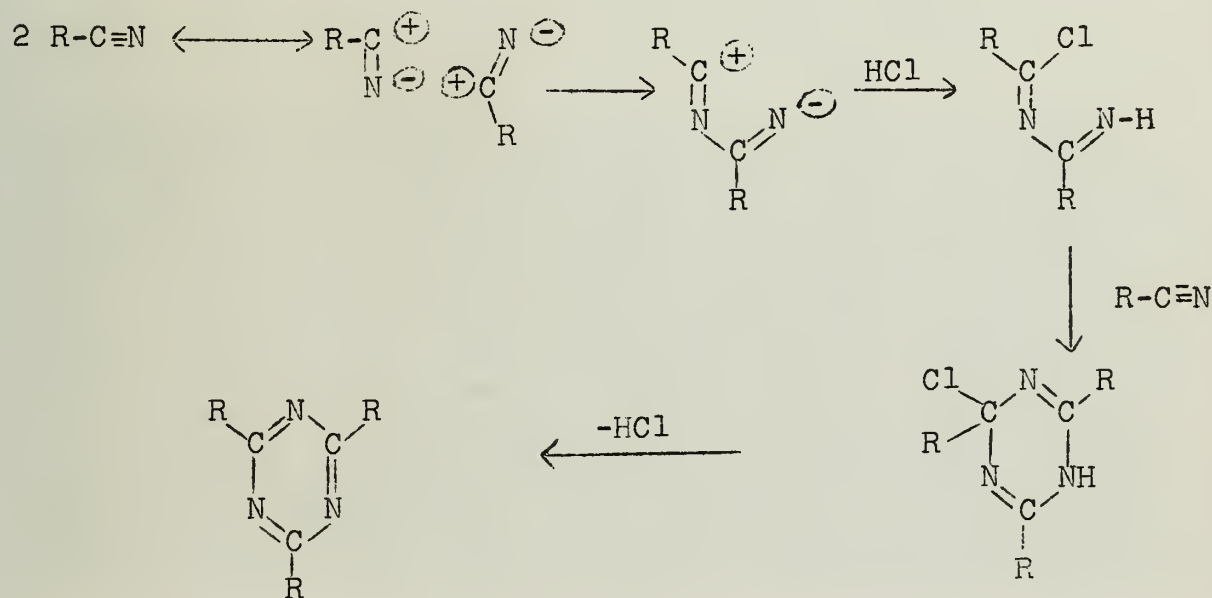
Reported by Fred P. Hauck, Jr.

March 18, 1955

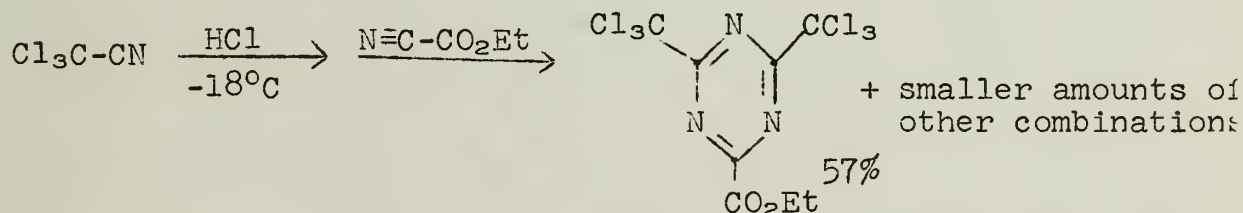
In contrast to olefinic compounds, which can form linear polymers of high molecular weight, simple nitriles appear to favor the cyclic trimeric state¹. Nitriles can thus be classified on the basis of their polymerization products:

1. S-triazine derivatives: nitriles with other functional groups attached to the nitrile group, e.g. HO-CN, H₂N-CN, X-CN, R-S-CN, ROOC-CN, or, those which bear no α-H-atoms, e.g., C₆H₅-CN, CX₃CN but not (CH₃)₃C-CN.
2. 4-amino-pyrimidine or 2,4-diamino-pyridine: nitriles bearing an α-methylene grouping, R-CH₂-CN, R=C₂H₅, C₆H₅; but not H or CH₃.
3. Higher polymers of unknown structure or not of trimeric nature: NC-CN and H-CN (basic conditions).

Polymerization of the first group under acid conditions may be pictured as a kind of Diels-Alder reaction²:



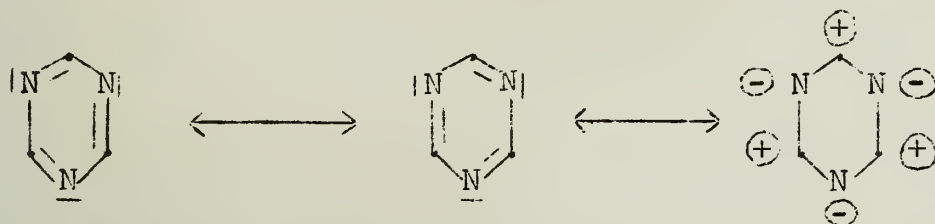
It has been shown³ that this reaction occurs with mixtures of nitriles to give variously substituted triazines, e.g.



In this way, nitriles which do not themselves polymerize can be used, e.g., CH₃-CN. Of chlorinated acetonitriles ClCH₂CN does not react while Cl₂CHCN and Cl₃CCN do, even though Cl₂CHCN bears an α-H-atom. Trimethyl acetonitrile also does not yield trimer. This is believed not due to steric hindrance, since triphenyl- and tris-(α-naphthyl)-s-triazine are well

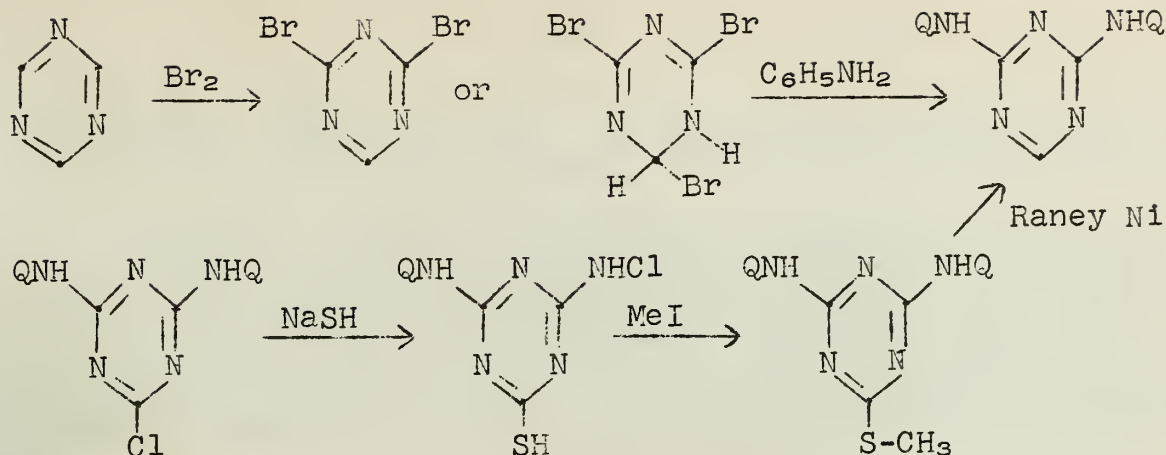
known, but to the inductive effect of substituents. In $\text{Cl}_3\text{C-CN}$ a partial positive charge is induced on a C-atom adjacent to a similarly charged C-atom; dimerization partially reduces the latter charge. In $(\text{CH}_3)_3\text{C-CN}$ the opposite I-effect is present which stabilizes the nitrile. A certain activation is also required in the dimeric state, for $\text{Cl}_2\text{CH-CN}$ trimerizes less readily than $\text{Cl}_3\text{C-CN}$ while ClCH_2CN and $\text{C}_6\text{H}_5\text{-CH}_2\text{CN}$ do not trimerize. The latter reacts only as far as $(\text{C}_6\text{H}_5\text{CH}_2\text{CN})_2 \cdot \text{HCl}$.

Although a great number of tri-substituted s-triazines are known, only a few di- and mono-substituted ones have been prepared and s-triazine itself has only recently been recognized⁴. From a consideration of the energy relations involved and by analogy with known pyridines and pyrimidines, s-triazine would be expected to have these principal resonance forms:

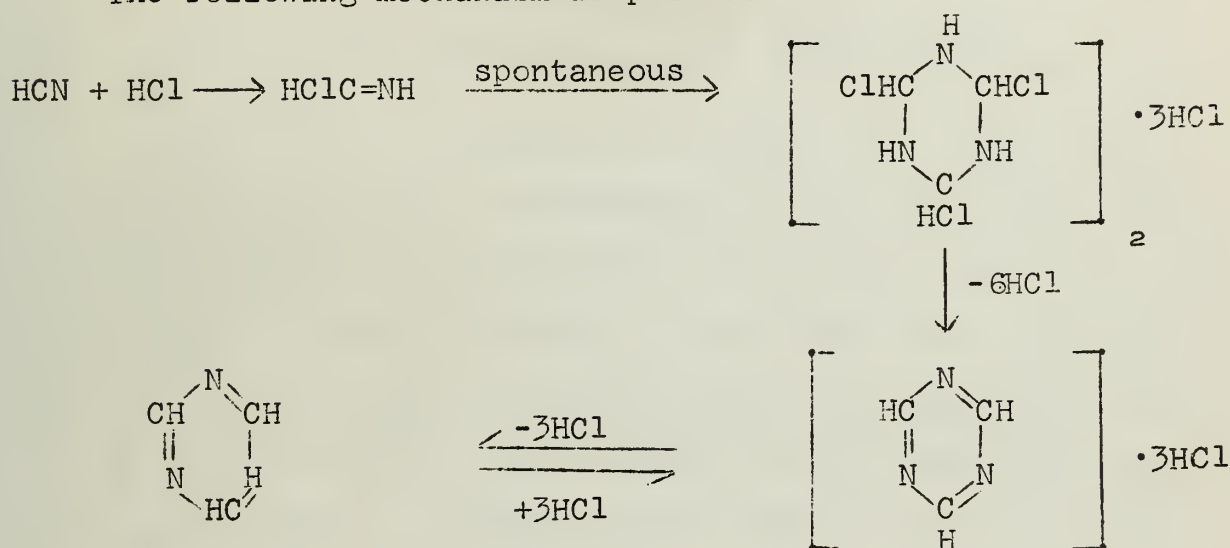


and most known s-triazines bear substituents which tend to stabilize the polarized form ($-\text{NR}_2$, $-\text{OR}$, $-\text{S-R}$, X , $-\text{NHNH}_2$, $-\text{N}_3$, $-\text{C}_6\text{H}_5$, $-\text{CH}_3$), while nitrotriazines, which would have the opposite effect, are still unknown⁵, although s-triazines bearing m-directing groups are known ($-\text{COOH}$, $-\text{COOEt}$, $-\text{CONH}_2$, $-\text{CN}$, $-\text{CX}_3$). The latter are very easily hydrolyzed however; $-\text{CN}$ and $-\text{CX}_3$ substituted s-triazines yield cyanuric acid and the others, oxalic acid. That resonance makes an important contribution to the structure is indicated by the shortening of the C-N bond in melamine and cyanuric acid and their high melting points. In fact studies of amino-triazines indicate that a primary amino group is not present, but that an imino structure is preferred^{6,7}. Free s-triazine, which does not possess stabilizing groups, should be reactive particularly in the polar form.

Grundmann *et al.*^{2,8-10} have recently demonstrated that the long-known "dimer of hydrocyanic acid" discovered by Nef¹¹ and later studied by Hinkel¹² is in reality the long-sought s-triazine. The structure C=N-CH-NH had been postulated, but the compound did not show properties of an isonitrile. A redetermination of molecular weight indicated a trimer, and mild hydrolysis yielded quantitative amounts of formic acid and NH_3 , which rules out any structure containing C-C or N-N bonds. Comparison of the I.R. and Raman spectra of simple substituted triazines along with the following conversion to known triazine derivatives all support the trimeric structure:



The following mechanism is postulated:



s-triazine is a solid, m.p. 86° , b.p. 114° , highly volatile, heat-stable, distillable from Na, but highly sensitive to solvolysis by -OH containing solvents. It forms addition products with silver and mercury salts. Its basicity is difficult to determine due to its ease-of-hydrolysis.

Chlorination yields chiefly cyanuric chloride and some dichlorotriazine. Bromination gives per bromide and, at higher temperatures probably dibromo-triazine (on the basis of derivatives). Reaction with NaNH_2 results only in NaCN and disodium cyanamide. s-triazine cannot be hydrogenated using noble metals as it is a powerful catalyst poison. Friedel-Crafts reaction yields only benzhydryl formamidine hydrobromide.

An intermediate of particular usefulness in the s-triazine series has been cyanuric chloride¹³ preparable from Cl_2 and HCN ¹⁴. This compound reacts like an acid chloride: hydrolysis yields cyanuric acid, treatment with phenols and alcohols gives triaryl and trialkyl cyanurates, respectively; with amines, substituted melamines. It also reacts with hydrazine derivatives, pyridines, sodium azide, and Grignard reagents. Wurtz-Fittig and Friedel-Crafts reactions are usable. With

carboxylic acids it yields cyanuric acid and an acid chloride. Replacement occurs with HX. It reacts with malonic ester to give a monosubstituted product.

Cyanuric chloride is resistant to catalytic reduction. With LiAlH_4 it forms 2-dimethylamino-4,6-dichloro-1,3,5-triazine and 2,4-dichloro-triazine in low yield. The former is due to hydrogenolysis of s-triazine formed initially from cyanuric chloride to dimethylamine, which then reacts with unchanged cyanuric chloride. Inorganic salts are the major product, however.

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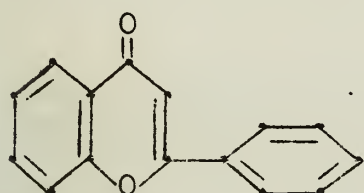
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THE FORMATION OF SUBSTITUTED FLAVONES BY THERMAL CYCLIZATION

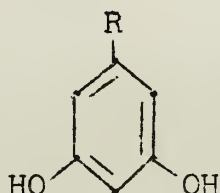
Reported by Bernard Freedman

March 25, 1955

Certain flavones in their natural state constitute the yellow pigments of plants and at one time were used as dyes. The interest in the flavones at present lies in their possible applications in the biogenetic and pharmacodynamic fields. Flavone (I) is 2-phenylchromone; the substituents most commonly found in flavones are -OH and -OCH₃.



I

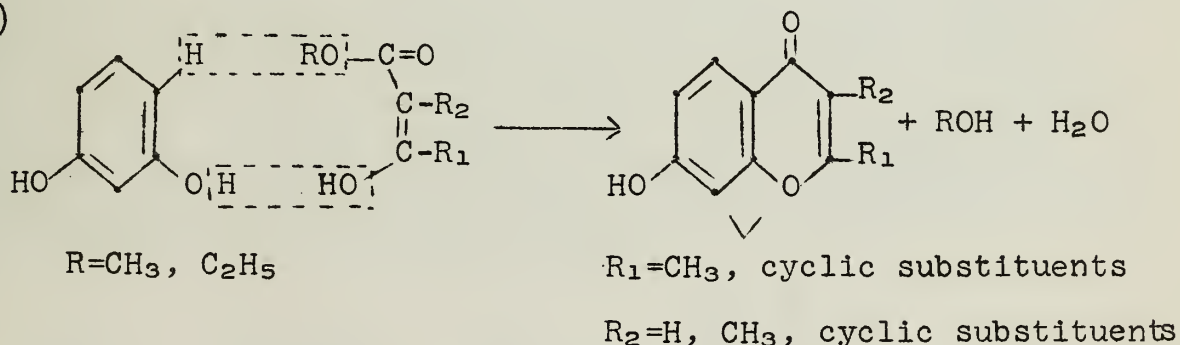


II R=H IV R=OH
III R=CH₃ XIII R=OCH₃

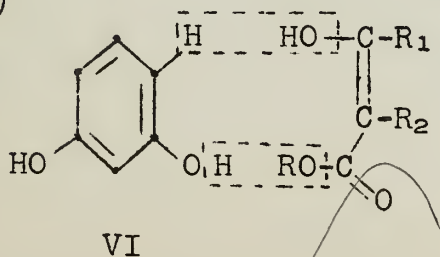
Although many of the natural chromones have been produced synthetically, the methods are often complicated and inefficient.^{1,2} A simpler approach was found by condensing a β-keto ester with a phenol. With 75% sulfuric acid as the catalyst coumarins were formed,³ whereas with phosphoric anhydride flavones resulted.⁴ More recently the condensation between β-keto esters and phenols to give flavones has been realized by thermal cyclization, which involves heating the reactants at 200-300°C in the absence of catalysts.⁵

In an effort to confirm the generality of this latter mode of condensation, Pillon treated various β-keto esters with resorcinol (II).⁶ Such a combination gives rise to coumarins or chromones and can occur theoretically in four different ways:

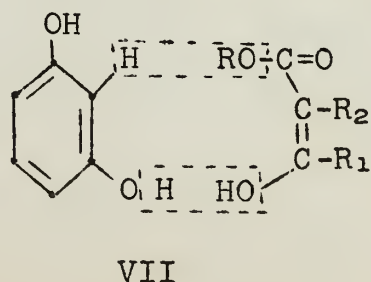
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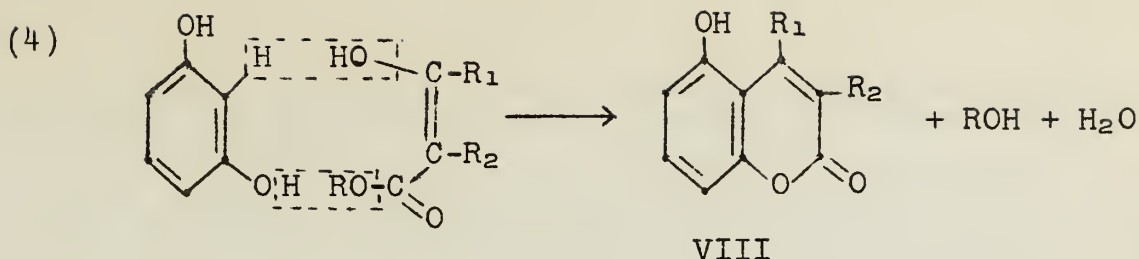


(2)



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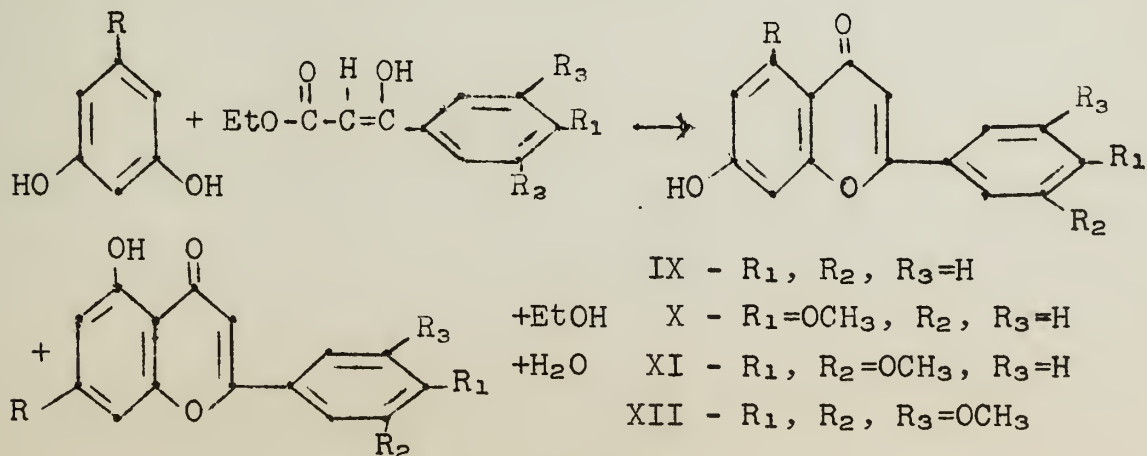


(1) (2) (3) and (4) would lead respectively to the 7-OH chromone (V), the 7-OH coumarin (VI), the 5-OH chromone (VII), and the 5-OH coumarin (VIII).

With five different β -keto esters, V was obtained in all cases accompanied by VI in three cases and VII in two cases. These results indicated that the first path (1) was the most important mode of condensation. Moreover, chromones were favored over coumarins unless simple aliphatic β -keto esters were used, in which case coumarins were favored.

When resorcinol was replaced by monophenols such as phenol or p-cresol the condensation failed. However, when α - and β -naphthols were treated with ethyl benzoylacetate (IX), the corresponding α - and β -naphthoflavones were obtained.⁷ These compounds had melting points and ultraviolet spectra identical with the same compounds obtained by other routes.^{8,9} With β -naphthol two cyclization paths are possible. The first involves the 1-H and the second the 3-H of β -naphthol. Only the product corresponding to the first path was isolated. The most recent work in the naphthols has been the condensation of 1,5-dihydroxynaphthalene with IX to yield 7,8-(o-hydroxybenzo)-flavone.¹¹

In order to compare the reactivity of resorcinol with other polyphenols, orcinol (III) and phloroglucinol (IV) were employed.¹⁰ Each of these three polyphenols was treated with various ethyl benzoylacetates. These keto esters were prepared by the Claisen condensation from aryl methyl ketones and ethyl carbonate in the presence of sodium.¹² The β -keto esters were the ethyl esters of benzoylacetate (IX), anisoylacetate (X), veratroyl acetate (XI), and 3,4,5-trimethoxybenzoylacetate (XII), which also permitted a comparison of the reactivity of these β -keto esters. These condensations are represented by the following scheme:



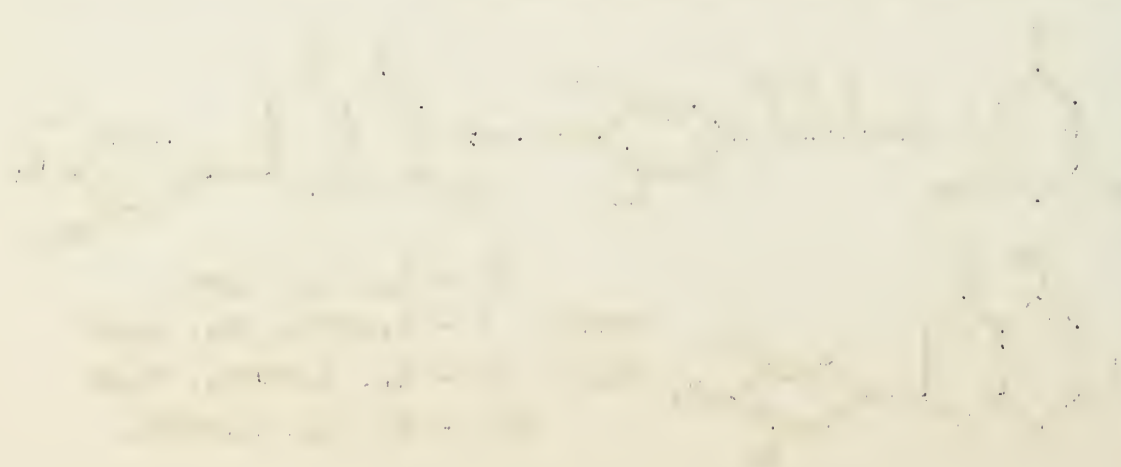


THE UNITED STATES OF AMERICA
DEPARTMENT OF THE INTERIOR
BUREAU OF LAND MANAGEMENT

TO THE SECRETARY OF THE INTERIOR
WASHINGTON, D. C.
FROM THE DIRECTOR OF THE BUREAU OF LAND MANAGEMENT
SALT LAKE CITY, UTAH
SUBJECT: [Illegible]

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By an examination of the products and yields of these reactions, the following orders of reactivity were established:

- (1) phenols: resorcinol > orcinol > phloroglucinol
- (2) esters: IX > X > XI > XII

The most recent work in this connection has been the condensation of XIII with IX and X.¹¹ As in the case of resorcinol, the 7-OH flavone is strongly favored over the 5-OH flavone.

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POLAR EFFECTS ON FREE RADICAL REACTIONS

Reported by Wendell W. Moyer, Jr.

March 25, 1955

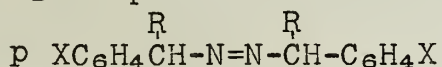
Introduction. The influence of polar factors, which play such an important part in ionic-type organic reactions, is much less clear in the case of free-radical reactions. It has only been within recent years that direct experimental results have been obtained on this subject.

Copolymerization. The effects of meta and para substituents on the reactivity of styrene in copolymerization reactions were among the first clearly defined examples of polar effects on a free radical reaction.¹⁻⁴ The results obtained correlated well with the Hammett rho-sigma equation.

Homolytic Dissociation. A. Experimental results to date indicate that the effects of substituents on the formation of carbon radicals cannot be correlated with the Hammett equation.

1. Hexaphenyl ethanes--all substituents increase the dissociation constant.⁵

2. Decomposition of azo-bis-1-aryllkanes.⁶



(R=CH₃, C₂H₅, (CH₃)₂CHCH₂ ; X=H, CH₃, CH₃O, Cl, C₆H₅)

All X substituents increase the rate constant slightly.

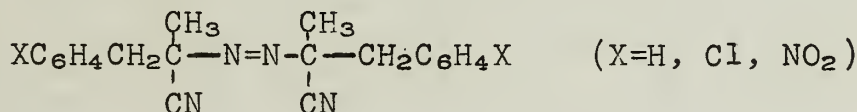
3. Decomposition of substituted benzyl bromides.⁷



(X=Cl, Br, NO₂, CH₃, CN)

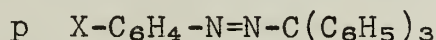
Substituent effects on bond dissociation energy are very small indeed and may not be attributed to polar factors as such.

4. Decomposition of azo-bis-nitriles.⁸



Little or no effect of substituents was observed.

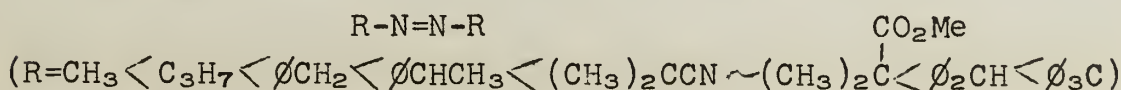
5. Decomposition of substituted phenyl-azo-triphenyl-methanes.⁹



(X=H, CH₃, Br, NO₂, HO, CH₃O, CH₃CONH)

Except for methyl, all substituents decrease the decomposition rate--phenyl conjugation is apparently the determining factor.

6. Decomposition of alkyl azo compounds.⁹



Decomposition rates increase in the order listed above--radical stabilization is believed to be the chief influence.

B. However, other radical systems have proven more amenable to the Hammett equation.

1. Decomposition of para substituted benzoyl peroxides.^{4,10}

Electron repelling substituents increase the decomposition rate while electron-attracting substituents retard. The data fit the Hammett equation closely.

2. Dissociation of para substituted 1,1,4,4-tetra-phenyl 2,2-dibenzoyltetrazanes.⁵

The dissociation constants of tetrazanes are strongly influenced by substituents and show a fine correlation to the Hammett equation.

Reactivity of Alpha-Phenyl Methylenic Compounds.

1. Substituted phenyl radical attacks on benzotrichloride. Electron withdrawing substituents decrease the ratio of side chain attack to nuclear attack.¹¹

2. Reactivity of substituted toluenes toward succinimidyl radicals¹² in bromination by n-bromosuccinimide.

Electron withdrawing groups decrease reactivity; while electron-releasing groups increase reactivity. Substituents obey the Hammett equation. (Rho value=-1.5)

3. Reactivity of substituted toluenes toward bromine atoms.¹²

Substituent effects were not quite so strong; although the Hammett equation was obeyed (Rho value=-1.0)

4. Reactivity of substituted cumenes toward trichloromethyl radicals.¹² Substituent effects were negligible.

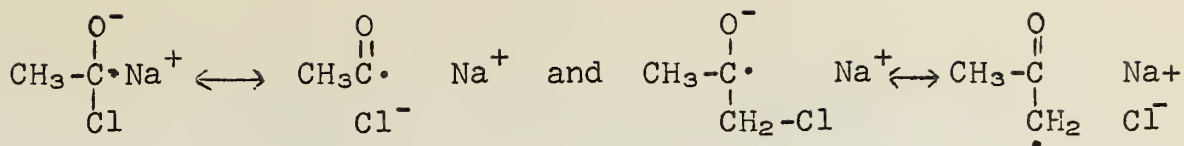
Considering the latter three examples, substituent effects were more important in reaction with succinimidyl radicals than with bromine atoms and were negligible with $\cdot\text{CCl}_3$. The sequence is the same as Paulings Electronegativity Scale where $\text{N}=3$, $\text{Br}=2.8$ and $\text{C}=2.5$. The evidence indicated the existence in the transition state of polar resonance forms between "donor" and "acceptor" type molecules.

Aliphatic Free Radical Reactions.

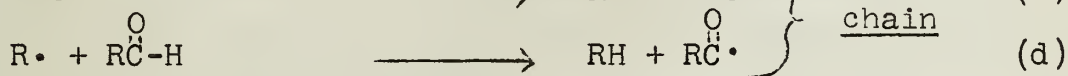
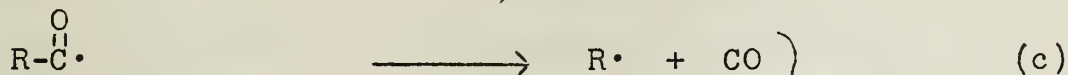
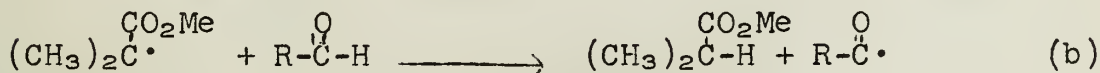
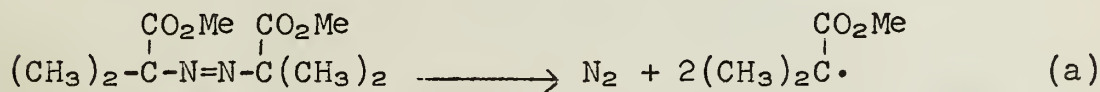
1. Reaction of isobutyric acid with methyl radicals and with chlorine atoms.^{4,13}

Using α -deuteroisobutyryl chloride, it has been conclusively shown that methyl radicals have a high selectivity for the α -hydrogen compared to chlorine atoms. The results are explainable on the basis of electrical effects in the transition complex.

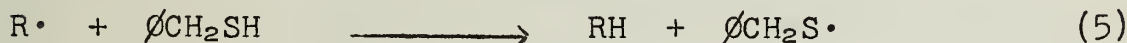
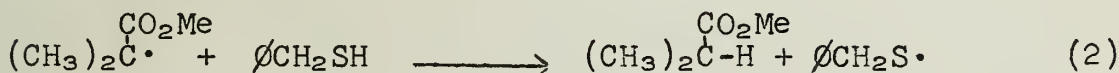
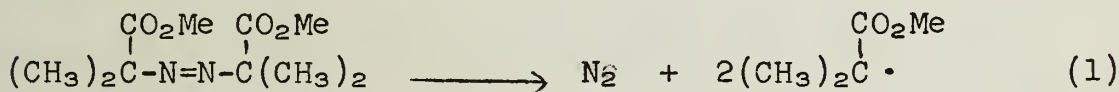
2. Gas phase reaction of sodium with alkyl halides.¹⁴ Electron withdrawing substituents are found to increase the rate of reaction of electropositive radicals such as sodium with alkyl halides. The additional ionic structures shown below are responsible for the high rate of reaction of acetyl and acetyl chlorides compared with what would be expected from bond-energy considerations.



3. Thiol catalyzed decarbonylation of aldehydes.¹⁵⁻¹⁹
Dimethyl α,α' -azo-isobutyrate decomposed thermally in aldehyde solutions results in a small amount of aldehyde decarbonylation as follows:



Thiols were found to have a strong catalytic effect on this decarbonylation reaction. The new reaction sequence is as follows:



The introduction of a mercaptan increases the amount of reaction since the substitution of two "donor-acceptor" type reactions (3) (5) for one "two donor" type reactions (d) has improved efficiency and reasonable ionic structures contributing to the stability of the two transition states may be written:



4. Hydrogen transfer by thiols.²⁰

In the system containing α,α' -azoethylbenzene, n-octanethiol and 9,10-dihydroanthracene, only one mole of thiol disappears for every four moles of ethyl benzene formed.

Conclusion

1. No fundamental difference exists between substituent influences on chemical reactivity in homolytic and heterolytic processes.

2. Inherently there may be a greater tendency for molecules to undergo polar reactions than electrically neutral type reactions.

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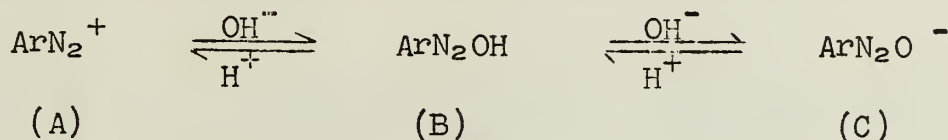
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REACTIONS OF THE DIAZONIUM ION AT VARIOUS pHs

Reported by A. J. Reedy

April 1, 1955

The diazonium ion may be considered as a dibasic acid, according to the equilibria:^{1,2}



Wittwer and Zollinger¹ have attempted to measure the equilibrium constants for diazotized p-chloroaniline and metanilic acid, and to determine changes in the relative concentrations of A, B and C with changes in pH. The shape of the neutralization curves for these compounds indicated that they react as dibasic acids for which $K_{a1} \ll K_{a2}$. Values for the term $\frac{\text{p}K_{a1} + \text{p}K_{a2}}{2}$ were determined from the pH value at the middle point of the neutralization curve, corresponding to 50% neutralization of the acid. The concentrations of A and C then may be found from the equation:¹

$$\text{pH} = \frac{\text{p}K_{a1} + \text{p}K_{a2}}{2} + \frac{1}{2} \log \frac{[\text{ArN}_2\text{O}^-]}{[\text{ArN}_2^+]}$$

Wittwer¹ was not able to calculate separate values for $\text{p}K_{a1}$ and $\text{p}K_{a2}$, although Hantzsch and Davidson³ had earlier estimated K_{a2} for the benzene diazonium ion to be 1.25×10^{-3} .

The maximum concentration of B is given by:¹

$$[\text{B}] = \frac{1}{2} \text{Ca} \sqrt{\frac{K_1}{K_2}}$$

(Ca = Stoichiometric conc. of the diazo compound)

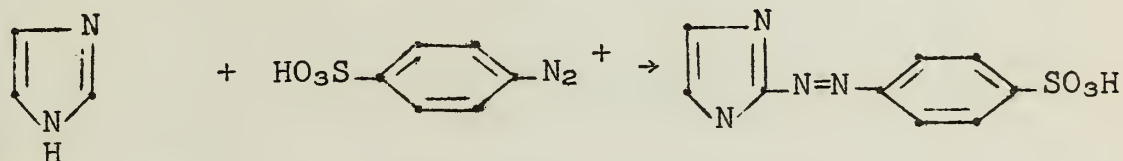
From this relationship it is seen that when $K_{a2} \gg K_{a1}$ (B) never appears in significant concentration.

Wittwer¹ determined that in the case of diazotized metanilic acid (A) begins to decrease when the pH is one unit smaller than $\frac{\text{p}K_{a1} + \text{p}K_{a2}}{2}$. One pH unit after this point, (A) falls to 1% of its initial concentration, and decreases 100 fold per pH unit thereafter.

In the reaction of diazotized metanilic acid with 2-naphthol-6-sulfonic acid the increase in coupling rate in the pH region 0-10 is due to the increase in the amount of 2-naphthol-6-sulfonic acid ($\text{p}K_{a2}$ 9.2) which exists as the bivalent negative ion. Throughout this pH region, the diazo compound is almost entirely in the form of the diazonium ion ($\text{p}K_{a1} + \text{p}K_{a2}$ for diazotized metanilic acid is 10.8). The decrease in coupling rate above pH 10 is due to a decrease in

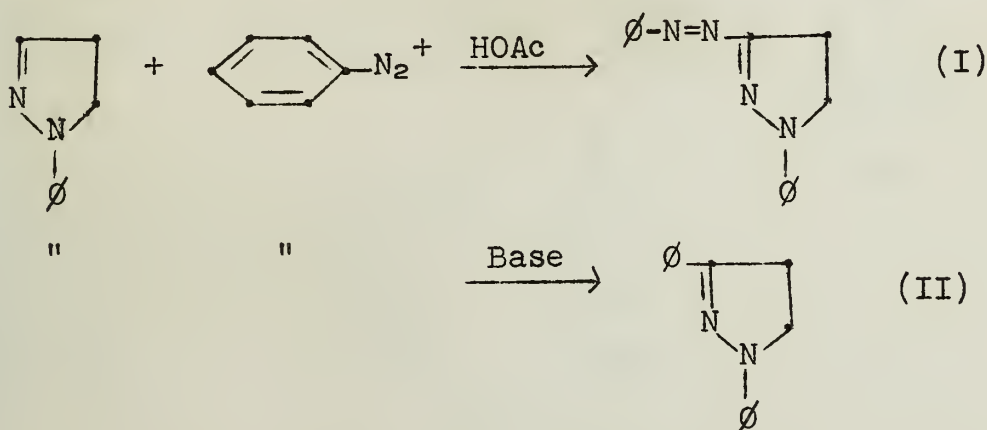
concentration of form A. The diazo compound exists in the form of C in this pH region. C does not undergo azo coupling.

R. D. Brown⁴ has found an increase in coupling rate within the pH range 7.1-11.0 for the following reaction:



(pK_{a2} = 12)

Duffin and Kendall⁵ found the reaction products to vary with pH in the following manner:



The second reaction, which proceeds rapidly at 0-10°, was found to be general for 1-aryl- Δ^2 -pyrazolines unsubstituted in the 3 position. The mechanism was not determined, although (I) can be excluded as an intermediate, since it is stable in alkaline solution.

Form B exists in such small concentrations in aqueous medium that nothing can be said about its coupling ability in this medium.¹ Huisgen⁷ studied the coupling action of diazoacetate in benzene and concluded that in the non-aqueous solvent the covalent form $\phi-N=N-OAc$ is the active coupling agent, and not the diazonium ion. This conclusion was based on the observation that the coupling rate was faster in benzene than in a mixture of benzene and acetic acid. The form $\phi-N=N-OAc$ predominates in benzene. The form

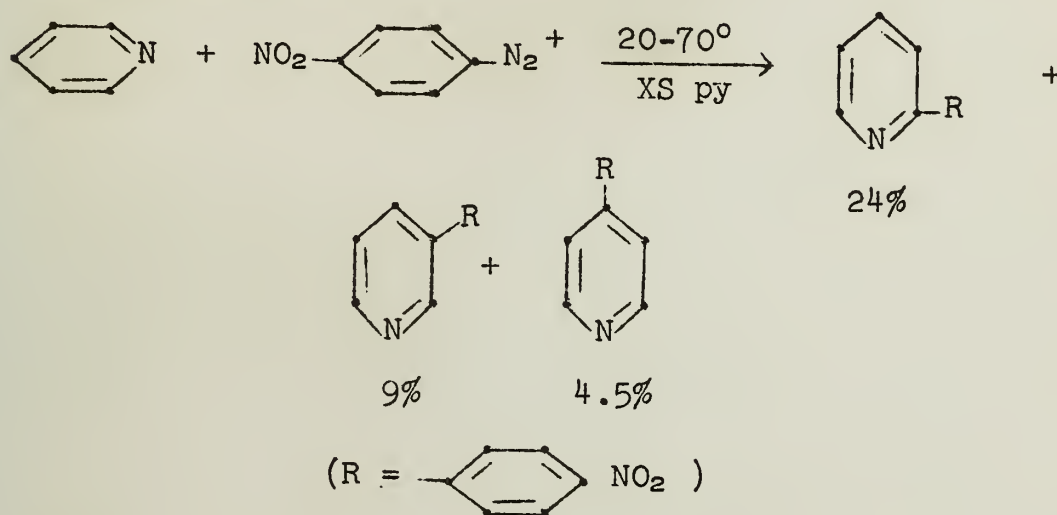
$\phi-N \equiv N^+ OAc^-$ predominates in benzene-acetic acid mixture.

Reactions which lead to biaryl coupling, as contrasted to azo coupling, include⁸--(1) Reduction of diazonium salts containing negative substituents, carried out in acid or alkaline solution; (2) Direct coupling of certain compounds in acid medium. Hirsch⁹, for example, obtained more than 50% yield of the *o*- and *p*-hydroxybiphenyls by treating benzene diazonium chloride with phenol in acid medium at 50-90° and extracting the product mixture with sodium hydroxide; (3) Use of dry diazonium salts and aluminum chloride in benzene.

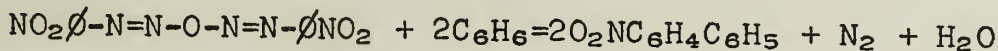
A Friedel-Craft type reaction produces biphenyl; (4) Coupling of diazo hydroxide in heterogeneous⁸ or homogeneous¹⁰ systems at pHs above 7.

Diazohydroxide coupling in all probability involves a non-ionic mechanism. This seems likely from the conditions under which the coupling is carried out in-particular, the use of a non-dissociating organic solvent of low dielectric constant, and by the fact that *o*-*p*-substitution almost invariably results, which would be difficult to explain on any ionic basis.

Haworth¹⁰ noted substitution in all three positions in the following reaction:



Haworth concluded that form B is the active coupling agent in this reaction. This conclusion could in part be supported by the observation that pyridine will not couple with the *p*-nitro benzene diazonium ion. It is not until an excess of the base has been added to neutralize the acid present in the diazonium salt solution that coupling begins. This parallels the formation of the diazo hydroxide. This does not eliminate the diazotate as the coupling initiator but the presence of α , β , and γ substituted products, and the absence of the normal polar directive influence of pyridine, would seem to favor a radical mechanism. Another possible initiator would be the diazo anhydride. Such anhydrides are formed upon a slow addition of alkali to an acid solution of a diazonium salt.⁸ The anhydride form leads to biaryl coupling in the following similar reaction:⁸



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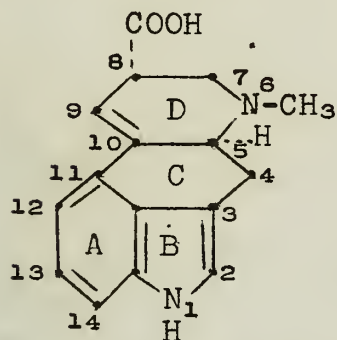
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THE STEREOCHEMISTRY OF LYSERGIC ACID¹
AND DIHYDROLYSERGIC ACID²

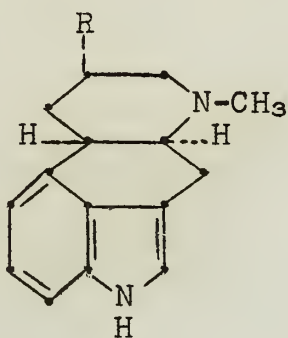
Reported by E. Tanda

April 1, 1955

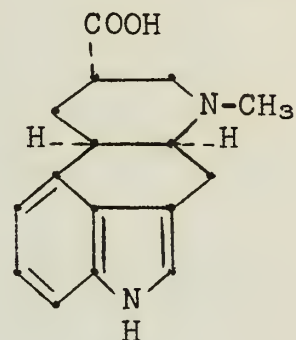
Recently, the stereochemical problem of lysergic acid and its related compounds which are the common constituents of the Ergot alkaloids³ have been discussed by several investigators.⁴⁻⁶



I Lysergic acid

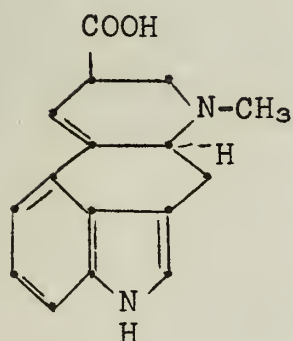


IIIa R=COOH
Dihydrolysergic
acid (I)

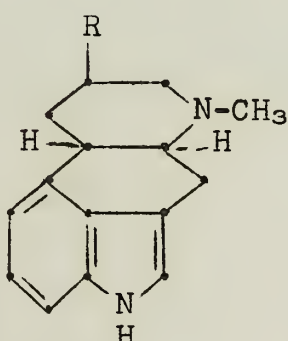


V
Dihydrolysergic
acid (II)

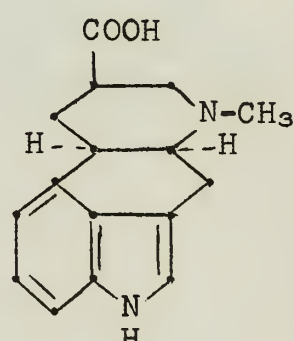
IIIb R=OH
6-Methyl,8-hydroxy
ergolin (I)
IIIc R=ACO
6-Methyl,8-acetoxy
ergolin (I)



II Isolysergic
acid



IVa R=COOH
Dihydroisolysergic
acid (I)



VI
Dihydroisolysergic
acid (II)

IVb R=OH
6-Methyl, 8 -isohydroxy
ergolin (I)
IVc R=AcO
6-Methyl, 8 -isoacetoxy
ergolin (I)

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Fig. 1.

Fig. 2.

Fig. 3.

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Fig. 4.

Fig. 5.

Fig. 6.

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THE JOURNAL OF THE
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In the dihydrolysergic acid series (III, IV, V and VI), the problem consists of two parts--the conformation of the substituent at C₈ (equatorial and axial) and the stereochemistry of the junction between the C and D rings (cis or trans). In III and VI, the faster rate of hydrolysis and the condensation reaction of the ester, the difficulty of elimination of the 8-amino group⁷ by HNO₂, the predominance of these isomers in epimerization equilibria and the stronger absorption in chromatography suggest that the substituents at C₈ are equatorial. In IV and V, the reverse facts suggest that the substituents at C₈ are axial.⁸ In catalytic hydrogenation, the fact that I produces only III but II produces IV and VI, can be explained as on the basis of the steric hinderance of the carboxyl group. Thus the C/D junction of III is trans and the C/D junction of the compounds formed on the hydrogenation of II are cis and trans.

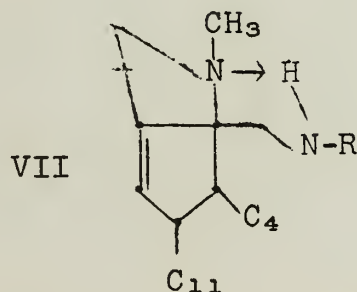
By a comparison of the infrared spectra of III, IV, V, VI with decalin series⁹ and steroid series¹⁰, the conformation assigned were confirmed. For example, IIIb, IVb, IIIc and IVc gave the characteristic absorption at 1037, 992, 1040 and 1020/35 respectively. These frequencies suggest that IIIb, IVb, IIIc and IVc have e-, a-, e- and a-substituent at C₈ respectively.

The assumption that the pK values depend chiefly upon the electrostatic effect satisfies the structures III through VI.

Table I

	III	IV	V	VI
pK ₁	4.85	4.45	4.67	4.97
pK ₂	7.85	9.25	9.28	8.38

In the isomerization equilibria between lysergic acid and isolysergic acid derivatives, the ratio between the I- and II-derivative is almost equal in the case of the primary amide derivatives, but I is predominant in the case of the secondary amide derivative. This is consistent with the following structure (VII).



The less stable form (axial-CONHR) can be stabilized by hydrogen bond formation. In 1953, R. C. Cookson⁴ suggested that ring D had the boat form but J. B. Stenlake has argued that ring D had the chair form. A. Stoll⁶ pointed out that the latter was more reasonable by the position between lysergic acid and dihydrolysergic acid. In pK values of lysergic acid amides, the hydrogen bond like VII is more effective although the electrostatic effect is recognized.

In general, lysergic acid derivatives are absorbed more strongly on alumina, except diethyl amide of dihydrolysergic acid (I).

Table II

		pK	Δ
Ergobasin	6.30	6.79*	0.25*
Ergobasinin	6.55	7.43*	0.64*
Lysergic acid ethylamide		6.09	
Isolysergic acid ethylamide		6.35	0.26
Lysergic acid diethylamide		6.37	
Isolysergic acid diethylamide		6.75	1.15
Dihydrolysergic acid (I) ethylamide (e)		6.68	
Dihydroisolysergic acid (I) ethylamide (a)		7.28	0.60
Dihydrolysergic acid (I) diethylamide (e)		6.79°	
Dihydroisolysergic acid (I) diethylamide (a)		8.87°	2.04

no mark 80% EtOH * H₂O ° 80% EtOH / 80% MeOH=4/1

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THEORY OF THE EARTH

The theory of the earth is a branch of geology which deals with the origin and development of the earth and its various parts. It is a science which seeks to explain the processes which have shaped the earth and its features. The theory of the earth is based on the study of the earth's history and its various parts. It is a science which seeks to explain the processes which have shaped the earth and its features. The theory of the earth is based on the study of the earth's history and its various parts. It is a science which seeks to explain the processes which have shaped the earth and its features.

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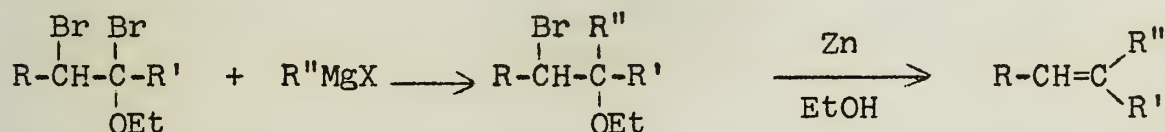
REACTIONS OF β -HALO ETHERS WITH METALS

Reported by Paul Tombouliau

April 15, 1955

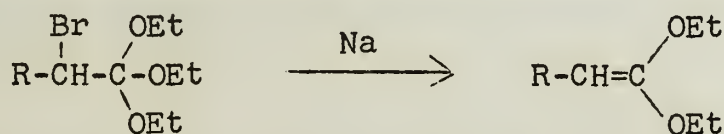
In 1904, Grignard reported that the reaction of β -bromophenetole with magnesium in ether gave abnormal products: phenol, ethylene, and a small amount of 1,4-diphenoxybutane.^{1,2} Wohl observed that the same reaction occurred when sodium was employed.³

The reaction of β -bromoethyl ethers with zinc in alcohol forms the basis of the generalized olefin synthesis which Boord developed.⁴ The reaction is general in scope, the yields are good (50-85%), and there are few, if any, by-products. A separable mixture of the cis and trans olefins is always formed.

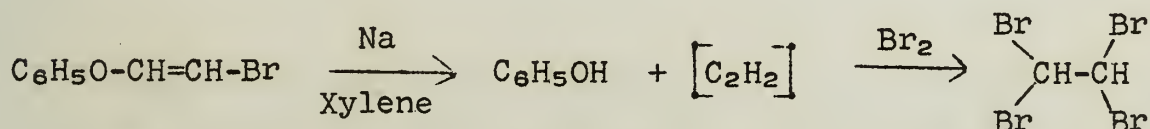


The reaction offers one of the few routes to certain 1,4-dienes, as well as to a variety of substituted ethylenes. Substituents in the α and β positions do not inhibit the reaction⁵, although the reaction fails for tetra-alkyl or tertiary alkyl ethylenes.

A synthesis of ketene acetals from α -bromoorthoesters has been accomplished using this method.⁶

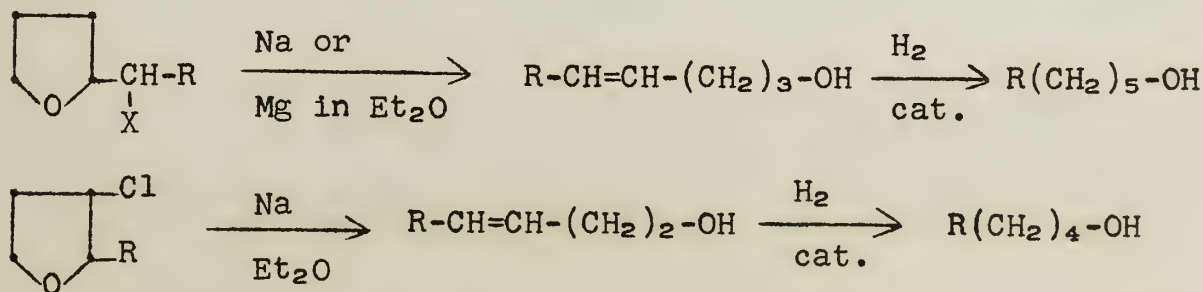


The analogy has been extended to the synthesis of acet-
ylenes.⁷

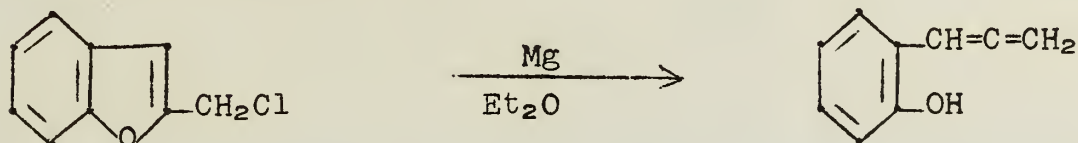


Magnesium in ether has been found to react with β -halo ethers in the same fashion as sodium.⁸

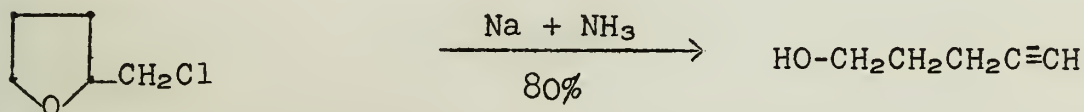
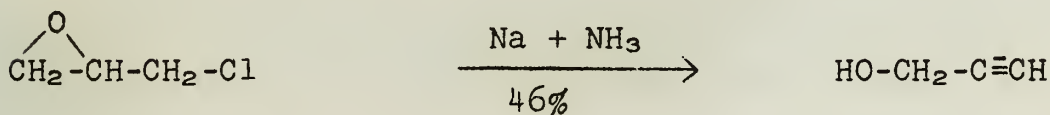
Ring opening of cyclic β -halo ethers occurs in an analogous way. The products are olefinic alcohols, which may be reduced to saturated alcohols, thus providing a convenient method for extending a carbon chain.^{9,10,11}



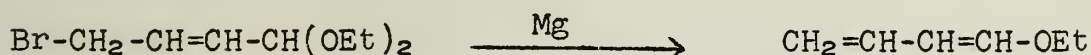
An especially interesting example of ring opening is the reaction of benzofurfuryl chloride with magnesium to form o-allenyl phenol.¹²



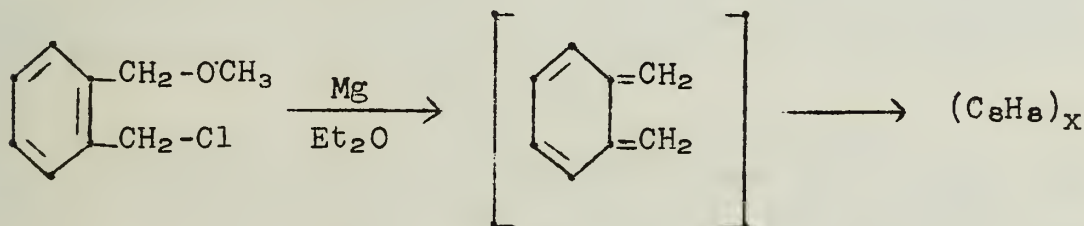
Sodium in liquid ammonia converts β -halo ethers to acetylenic alcohols. Examples of compounds easily prepared by this method are propargyl alcohol¹³ and 4-pentyn-1-ol.¹⁴



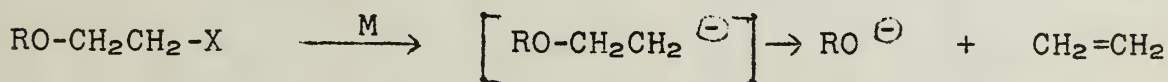
Vinylogs of halo ethers yield butadienes.^{15,16}



A remarkable example of this is the reaction of o-methoxymethylbenzyl chloride.¹⁷

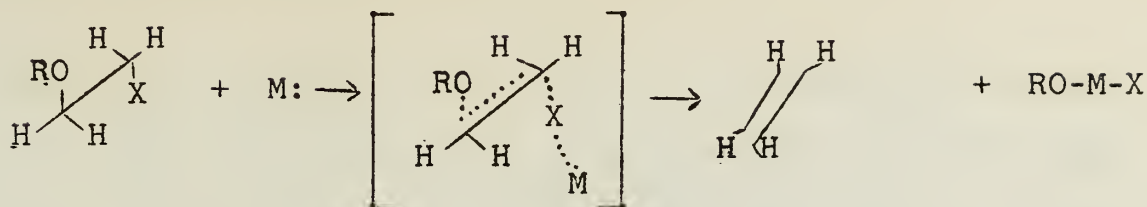


The mechanism of the reaction of β -halo ethers with metals has not been established. The reactions usually yield mixtures of the cis and trans elimination products. There is evidence against a stable Grignard-type carbanion. The Gilman test for a Grignard reagent is negative at all stages of the reaction, and attempts at carbonation have not been successful.^{8,17,18,19} If the reaction does involve a carbanion intermediate, β -elimination of a stable anion must occur rapidly.^{18,20}



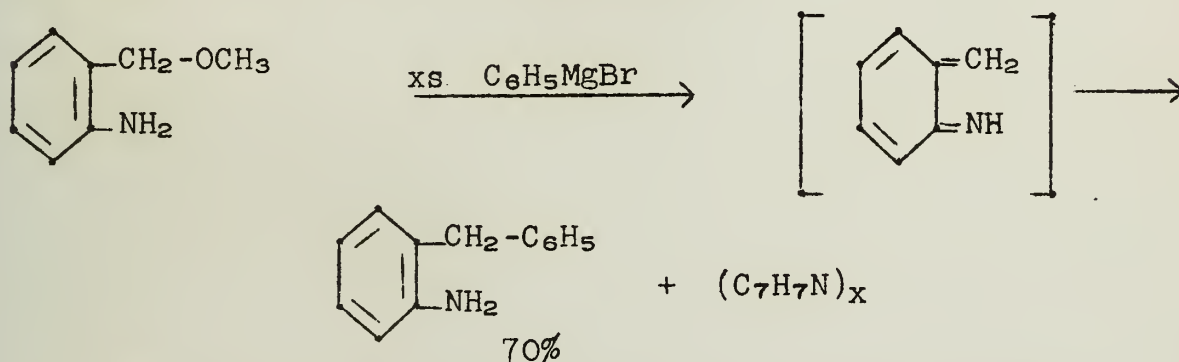
It is possible that the reaction may proceed in a manner similar to the debromination of vicinal dibromides when treated with metals.²¹ In the latter reaction, zinc and magnesium give stereospecific trans elimination, but sodium yields products formed by cis and trans elimination. The reaction of halo

ethers may be illustrated as follows:^{2,5,9,18}



β -halo sulfides and β -halo amines react with sodium in a manner similar to that of β -halo ethers. Both β -bromoethylphenylsulfide and N- β -chloroethylmorpholine yield ethylene.¹⁸

An extension of the reaction of *o*-methoxymethylbenzyl chloride with magnesium has been made recently by Mann and Stewart. When *o*-methoxymethylaniline is treated with a Grignard reagent, an addition product and a polymer are formed.²²



The reaction of β -halo ethers with sodium in ammonia appears to be of a different nature than with sodium alone, and as yet no satisfactory explanation has been offered.¹³

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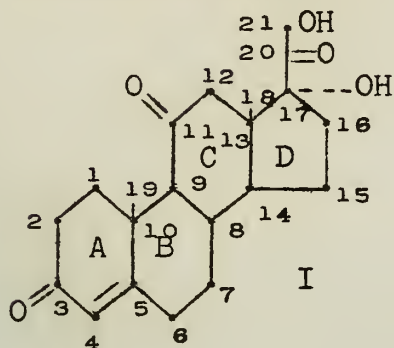
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SYNTHESES OF CORTISONE

Reported by George A. Gregoriou

April 15, 1955

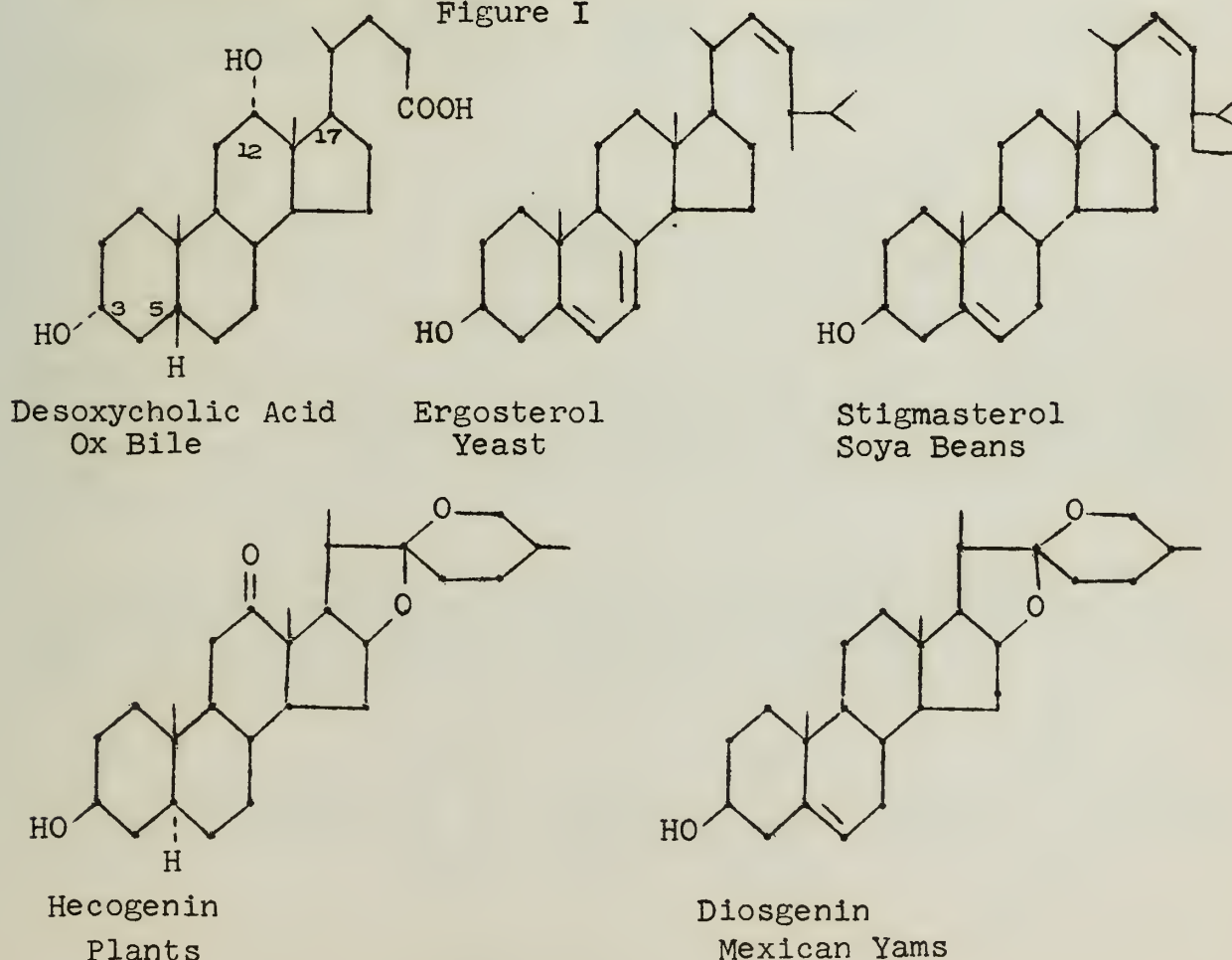


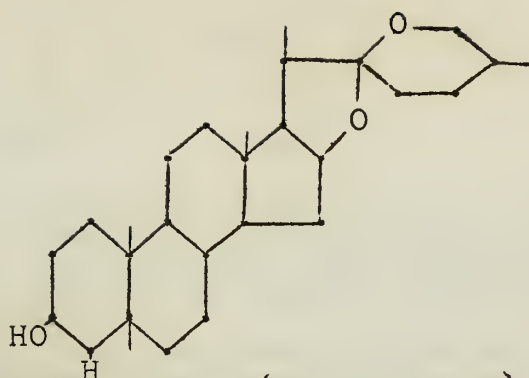
Interest in possible pharmacological applications of the adrenal cortical hormone cortisone (I) resulted in a 37-step partial synthesis¹ of the hormone from desoxycholic acid. This paper will be concerned only with the more important synthetic contributions to cortisone from a commercial or a potentially commercial standpoint.

The partial syntheses of cortisone from readily available steroids (Fig. I) are associated with four major problems, namely:

- A) Introduction of a C₁₁-keto group.
- B) Degradation of the C₁₇-side chain of the starting material.
- C) Construction of the dihydroxyacetone side chain.
- D) Introduction of the Δ^4 -3-keto moiety.

Figure I





Sarsasapogenin (Mexican Yams)

A) The chemical solutions of this problem utilize either 12-oxygenated steroids or ring B unsaturated steroids. The former are converted into the 11-keto compounds by an excellent method developed by Kendall^{2,3} which is applicable to steroids of the "normal" (cis A-B ring fusion) series only. A very useful transformation with an applicability not limited by the conformation at the A-B ring junction is that applied to hecogenin^{4,5} (Fig. II).

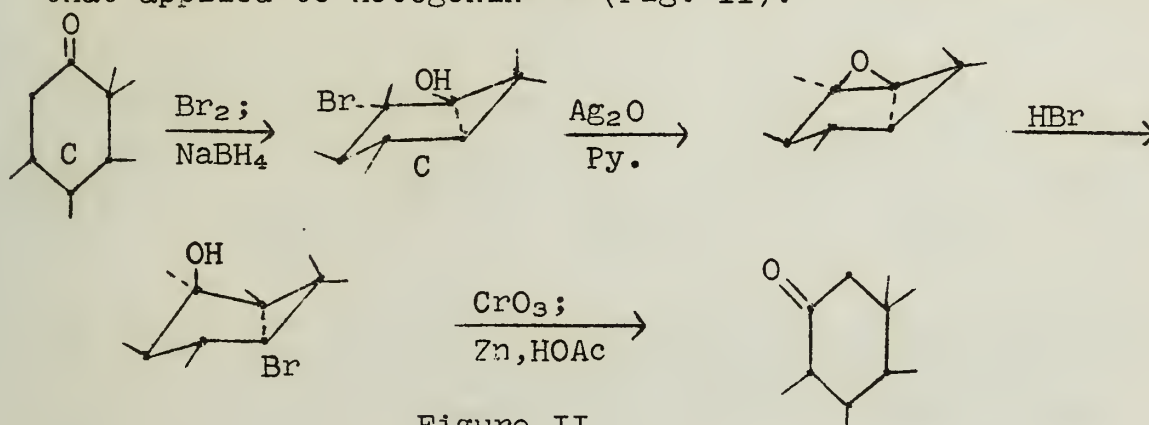


Figure II

[The scheme presented in this and in all other Figures focuses attention on the reactive centers of interest and omits the hydrolysis of ester groups as well as some transformations (e.g. esterification) necessary for the protection of other reactive centers.]

The conversion^{6,7,8} of ring B unsaturated steroids into 11-oxygenated compounds involves an initial introduction of the 7:9(11) diene system. The best of these methods is perhaps that applied by Jones⁷ on ergosterol (Fig. III)

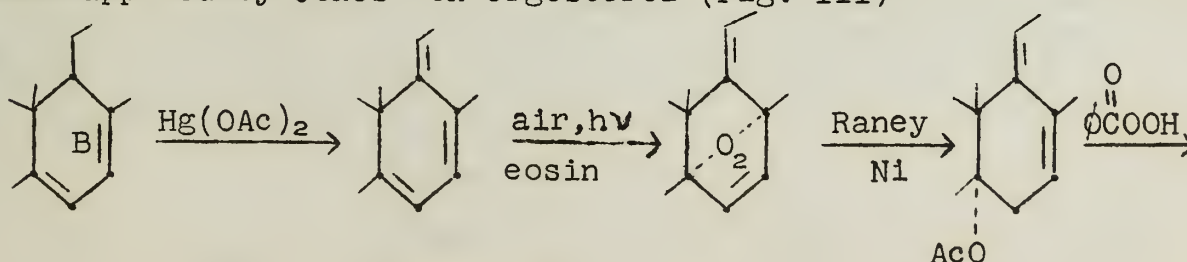
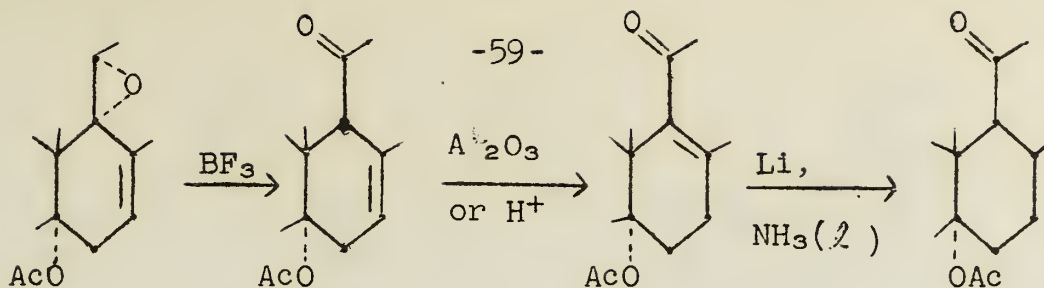


Figure III

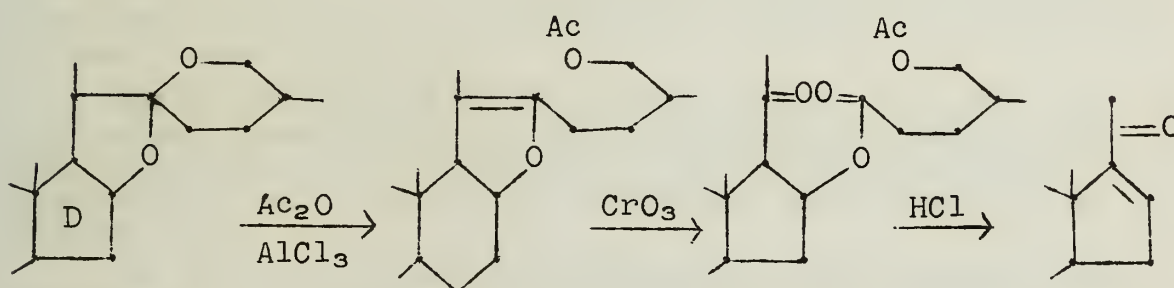


B) The three types of C_{17} -side chains lend themselves to degradation with different ease. In the bile acid series, the most efficient degradation is the Wettstein's modification⁹ of Miescher's method.

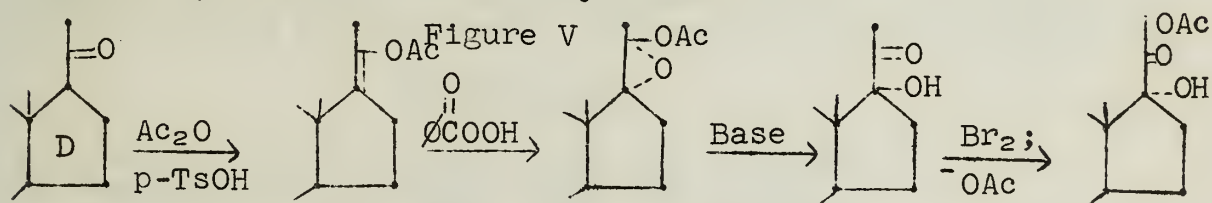
The side chain degradation of ergosterol or stigmasterol is best¹⁰ accomplished by ozonolysis to an aldehyde and subsequent oxidation of the "enamine" (enol amine) of this aldehyde.

Easiest among the degradations is that (Fig. IV) of the spiroketal type of side chain present in diosgenin¹¹.

Figure IV

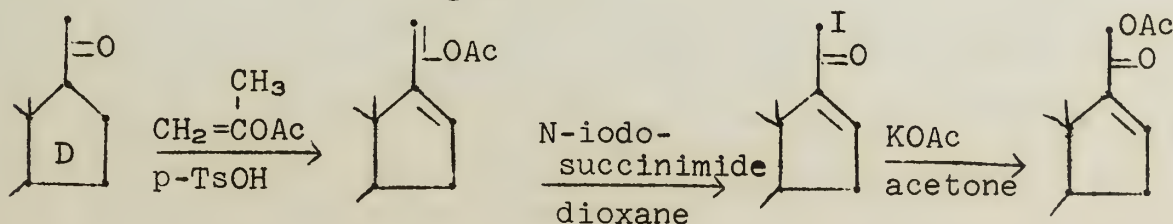


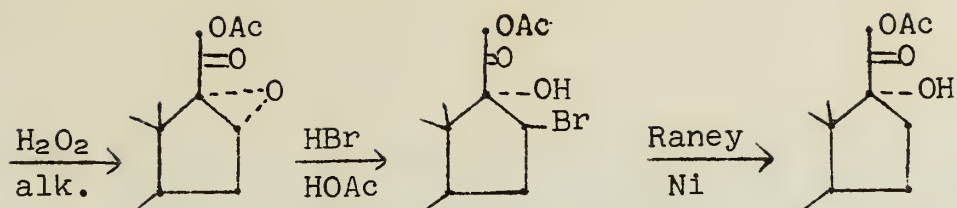
C) All the successful methods of building the dihydroxyacetone side chain have depended on intermediates having a 17(20) or a 16 double bond. Gallagher's method¹² (Fig. V) is perhaps the most successful one, although Sarett's cyano-hydrin synthesis is also very useful.



An alternative to Gallagher's synthesis applicable to Δ^{16} -20-ketones (normal products of the degradation of the spiroketal side chain, also obtainable from saturated 20-ketones by Colton's method¹³) is the method first devised by Julian and later modified. This procedure coupled with the work of Moffett and of Djerassi¹⁴ offers a useful route (Fig. VI) to the dihydroxyacetone side chain.

Figure VI





D) The introduction of the Δ^4 -3-keto moiety has been accomplished¹⁵ in the "allo" (trans A-B ring fusion) series in poor yield but it has met with much greater success¹⁶ with the "normal" derivatives. The method employed with the "normal" compounds involves oxidation to a 3-keto group, bromination to the 4-bromo derivative and dehydrobromination with semicarbazide. However, an initial one-step oxidation-chlorination¹⁶ with t-butyl hypochlorite leads to better yields.

Three total syntheses¹⁷ of cortison have been developed. Although very interesting chemically, they are not of any practical significance at the present time.

An important contribution to synthetic organic chemistry is the development of microbiological hydroxylation methods¹⁸. Such hydroxylation at the important 11α -position was first achieved by Peterson in 1951 and was followed by oxygenation at many other positions¹⁸.

Among the several economically attractive routes to cortisone, opened^{18a} by the 11α hydroxylation method, the most attractive one¹⁹ utilizes as the starting material progesterone which is readily available from diosgenin or ergosterol¹⁰.

The microbiological hydroxylations have recently been extended to the important 17α -^{20,21} and 21 -²⁰ positions.

The field of biosynthesis of the adrenal cortical hormones has also expanded²² considerably during the last two years. Thus, according to Samuels²³, hydroxylations of steroids by enzymes of the mammalian glands at positions 17, 21, 11 proceed in this order only and not in the reverse one.

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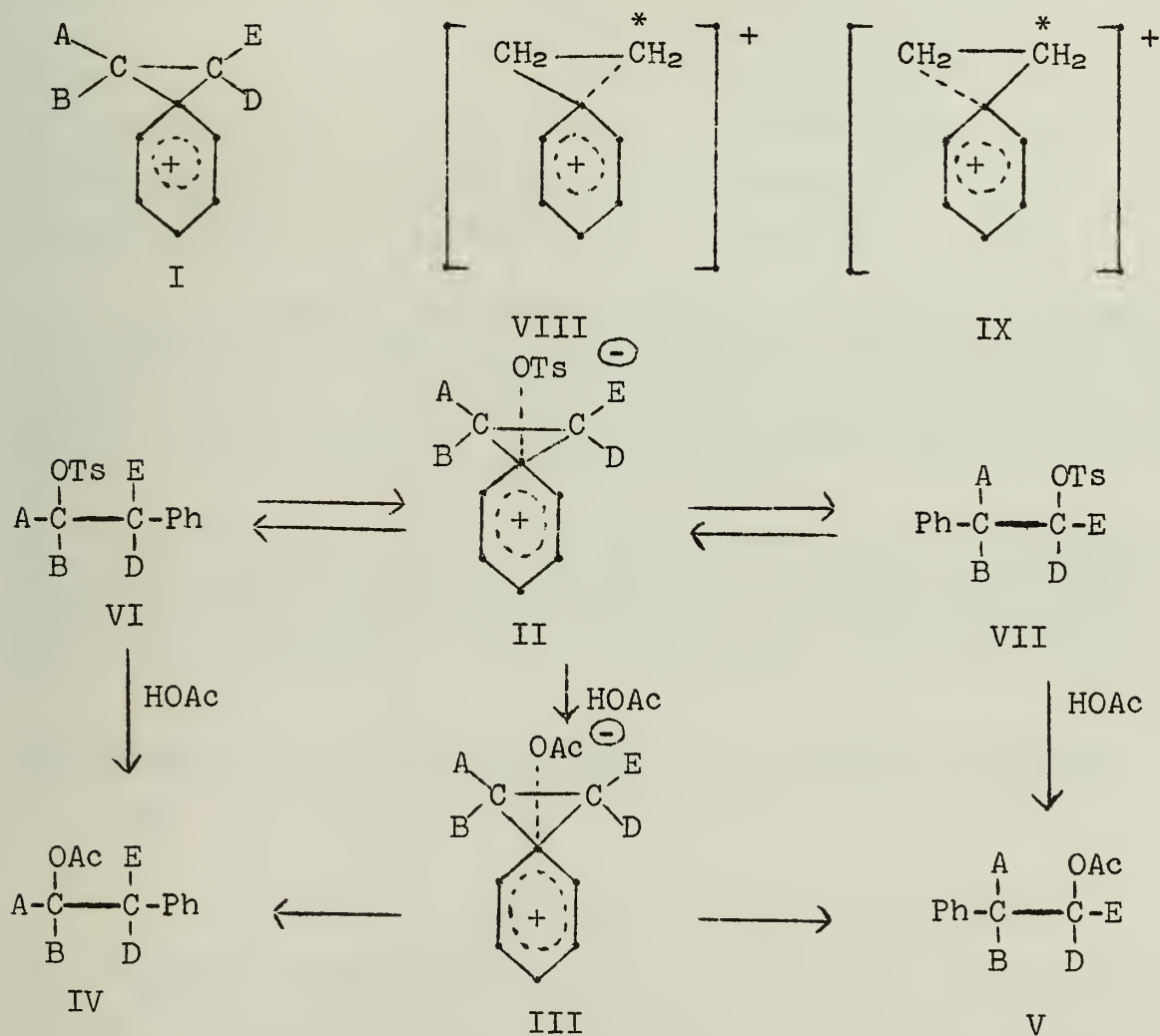
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THE PHENONIUM ION CONCEPT

Reported by A. J. Lauck

April 22, 1955

In 1949 Cram¹ introduced the concept of the symmetrical phenonium ion I as a discrete reaction intermediate (of geometrical stability) to explain the clear-cut stereochemical results with the diastereomeric 3-phenyl-2-butanols. Later the results² of solvolytic reactions of closely related systems led to the proposal that both open and bridged ions co-exist as intermediates. Also postulated^{3,4,5} was the view that the bridged cation existed in solution with the anion as an ion pair II which then reacts with the solvent to form a new ion pair III, followed by collapse to form the products IV and V. Winstein⁵ extended this proposal to include the collapse of ion pair II to form the two possible open chain compounds VI and VII which may then react to form the products. On the basis of radiochemical experiments on the nitrous acid deamination of 2-phenylethylamine-1-C¹⁴ Roberts⁷ proposed structures similar to VIII and IX as cationic intermediates.



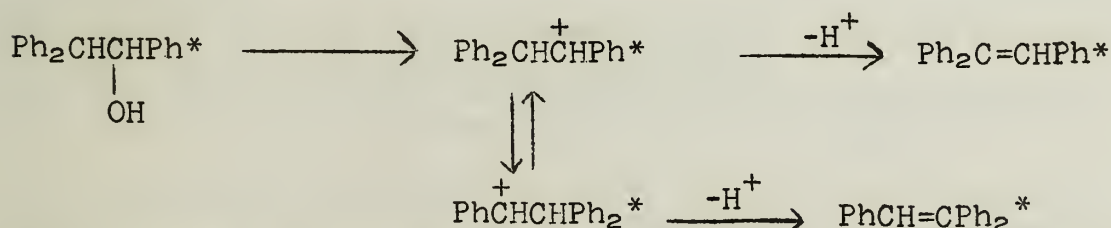
Recently Bonner and Collins^{8,9} have studied a number of irreversible processes using a radiochemical double-labeling technique in the 1,2,2-triphenylethyl system. A comparison was made of the distributions of the radioactive labels when derivatives of 1,2,2-triphenylethanol-1-C¹⁴ and of 1-phenyl-C¹⁴-2,2-diphenylethanol undergo certain irreversible carbonium

ion-type reactions. The reactions fall into two categories: one, those in which a statistical distribution of radioactivity was found in the product (1-4); and two, those in which a statistical redistribution has been approached, but not achieved (6-11).

<u>Labeled Compound</u>	<u>Reagents</u>	<u>Product</u>	Percent of Label C ¹⁴ in Oxidation Products	
			<u>Ph₂CO</u>	<u>PhCOOH</u>
Ph ₂ CHC*H(OAc)Ph	HCOOH, p-TSA	Ph ₂ C=CHPh	50.0	49.2
Ph ₂ CHCH(OAc)Ph*	HCOOH, p-TSA	Ph ₂ =CHPh	66.3	33.2
Ph ₂ CHCH(OAc)Ph*	HCOOH	Ph ₂ C=CHPh	65.8	33.5
	+ Ph ₂ CHCH(OCO)Ph		66.0	----
Ph ₂ CHCH(OH)Ph*	HCOOH	Ph ₂ C=CHPh	65.3	33.7
Ph ₂ C=C*HPh	HCOOH	Ph ₂ C=CHPh	0.72	----
Ph ₂ CHC*H(OTs)Ph	HOAc, NaOAc	Ph ₂ CHCH(OAc)Ph	39.5	59.3
Ph ₂ CHCH(OTs)Ph*	HOAc, NaOAc	Ph ₂ CHCH(OAc)Ph	47.1	51.7
Ph ₂ CHC*(OTs)Ph	H ₂ O, Acetone	Ph ₂ CHCH(OH)Ph	22.2	74.4
Ph ₂ CHCH(OTs)Ph*	H ₂ O, Acetone	Ph ₂ CHCH(OH)Ph	23.6	73.8
Ph ₂ CHC*H(OH)Ph	p-TSA, Xylene	Ph ₂ C=CHPh	47.9	52.4
Ph ₂ CHCH(OH)Ph*	p-TSA, Xylene	Ph ₂ C=CHPh	60.2	----

In the absence of internal return (collapse of ion pair II), symmetrical phenonium ions cannot be the sole cationic intermediates in the reactions (1-4). Such a mechanism would require an equal distribution of radioactivity between the two phenyl-labeled products in each case, rather than the observed 2/3 - 1/3 statistical distribution.

A mechanism in which the open carbonium ion intermediate undergoes radiochemical isomerization and then ultimately suffers either nucleophilic attack by a foreign molecule or ion, or proton loss to yield irreversibly the final product has been proposed.⁹



The extent of redistribution of the radioactive label during each reaction depends upon the ratio of the rate of phenyl migration in the cationic intermediate to the rate of nucleophilic attack by the solvent (or the rate of proton loss by the cation). A kinetic relationship involving the equilibrating cationic intermediates can be derived for the reactions (6-11), which allows a calculation of the radiochemical redistributions in the chain-labeled series, knowing the amount of carbon-14 migration attending reaction in the ring-labeled series. These calculations check within experimental error with the observed

values, thus substantiating the possibility of the proposed mechanism.

Stereospecificity has been demonstrated in the pinacol-type rearrangements¹⁰ and to a high degree in the Wagner-Meerwein¹¹ rearrangement of D-(+)-1,1-diphenyl-2-propanol. In considering a bridged-ion, stereospecificity can only be explained in terms of a trans-phenonium ion rather than the cis-isomer. Under these conditions, the amount of radiochemically rearranged products in the phenyl-labeled series should exactly equal the amount of rearranged product in the chain-labeled series. This was not observed, thus ruling out the bridged ion concept as the sole intermediates. Nor can such bridged cations be formed competitively with the open carbonium ions and then be disposed of directly by going to the product. Such bridged intermediates would lead to less than the observed amount of carbon-14 rearrangement in the phenyl-labeled series. Also the question of bridged ions formed directly from reactant in competition with the open ions, and then entering into equilibrium with the open ions has been found to be incompatible with the kinetic data. However, the surprising ease of interconversion of the open-chain cations in the proposed mechanism might be explained by assuming the intervention of a bridged-ion between the two classical ions. Such a rationalization would require a knowledge of the relative magnitude of the energy barriers involved.

In triple-labeling experiments,¹² 1,2,2-triphenylethyl acetate separately labeled in the chain, phenyl and acetate portions of the molecule and combinations of these three differently labeled species, kinetic data have been obtained with respect to the rate of radiochemical isomerization and of acetoxyl exchange under the influence of an acid catalyst. The rates of radiochemical equilibration of the ring-labeled and chain-labeled acetates are equal, and each is identical to the rate of loss of the labeled acetoxyl group which allows the following conclusions.

1. Internal return does not occur during the isomerization, since the rate of acetoxyl loss is the same as the rate of equilibration of the phenyl-labeled and chain-labeled acetates.
2. Symmetrical or unsymmetrical bridged ions can be ruled out as the sole cationic intermediates.
3. The above proposed mechanism involving the classical carbonium ion intermediates receives support.

It has been pointed out quite properly by Brown and Kornblum¹³ that the concept of non-classical or bridged-ions should be used with caution, lacking definite experimental evidence that these ions actually exist in the particular system under study.

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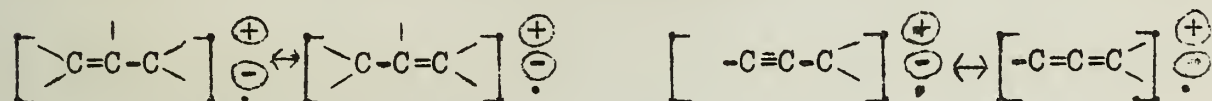
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THE INTERCONVERSION OF ALLENES AND ACETYLENES

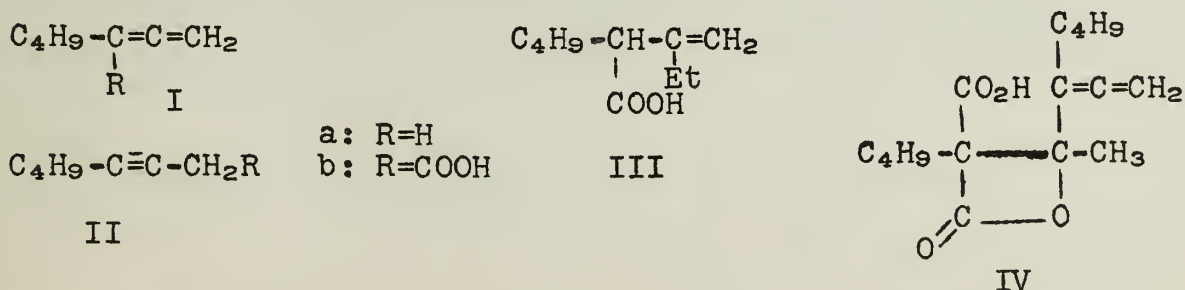
Reported by Duane F. Morrow

April 22, 1955

In 1887 Favorskii discovered that 1-alkynes, when heated with alcoholic alkali, were isomerized to 2-alkynes. He also found that 2-alkynes, or in some cases even acetylenes in which the triple bond was further removed from the end of the chain, when heated with sodamide, were converted into the sodium salts of the corresponding monosubstituted acetylenes. 1,2-Dienes were proposed as intermediates in these reactions. This idea was borne out by the rearrangement of isopropyl acetylene to 1,1-dimethylallene.¹ In 1935 it was discovered that the bromide prepared from a tertiary propargyl alcohol possessed unusual properties for the acetylenic structure assigned it.² Present evidence indicates that this compound was probably a haloallene. This isomerization of acetylenes and allenes is called the "propargylic rearrangement," by analogy with the similar allylic rearrangement, and is believed to occur with carbonium ions³, carbanions⁴, and free radicals.⁵



Grignard reagents prepared from propargyl halides react as though they exist as mixtures of propargyl and allenyl magnesium halides. Thus hydrolysis of the Grignard reagent prepared from 1-bromo-2-heptyne gave a 40% yield of the allene Ia and a 36% yield of the acetylene IIa. The Grignard reagent prepared from the secondary propargyl halide, 3-bromo-1-heptyne, likewise gave a mixture of hydrocarbons upon hydrolysis. The ratio of 1,2-heptadiene to 1-heptyne was 2.6 to 1. Carbonation of the former Grignard reagent yielded 41% of Ib, 9% of IIb, and a small quantity of a dimeric acid.^{6,7} The yield of this dimeric acid was increased at the expense of Ib by adding the dry ice slowly with stirring to the Grignard reagent. It was therefore suspected that the dimer was formed by attack of the Grignard reagent on the carbonated allenyl magnesium bromide salt.⁸ This theory was verified when it was discovered that an excess of ethyl magnesium bromide reacted with Ib to give III in 85% yield. This reaction probably proceeds by 1,4 addition of the Grignard reagent to the acid.⁹ The structure of the dimer formed by the carbonation of the Grignard reagent of 1-bromo-2-heptyne has since then been shown to be IV.⁸

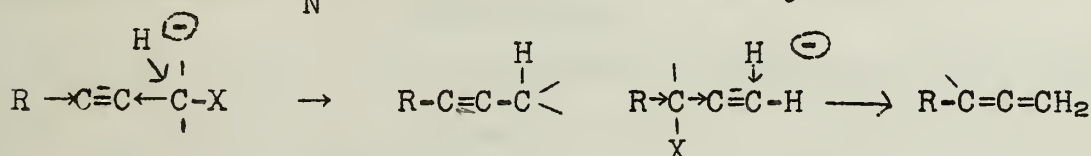


Treating propargyl halides with zinc also leads to allene derivatives. Allenes, contaminated only slightly with the isomeric acetylenes, are produced in 50-75% yield by the reduction of secondary propargyl halides with a zinc-copper

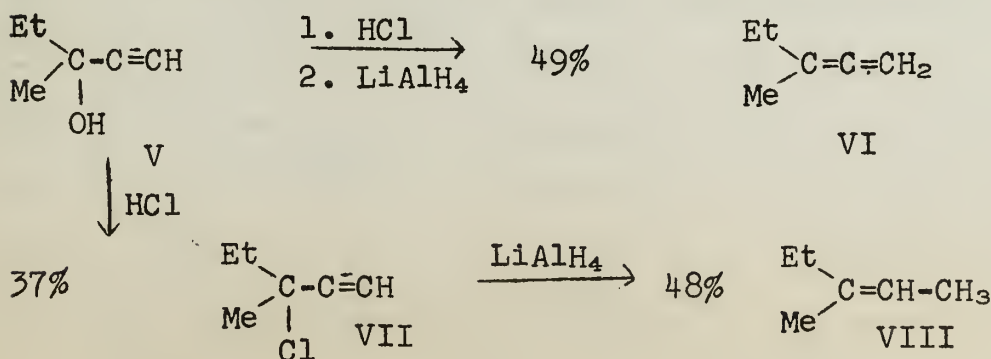
couple in ethanol.¹⁰ This constitutes one of the better methods of synthesis of these compounds. For example, reduction of 3-bromo-1-heptyne yielded 74% 1,2-heptadiene and only 3% 1-heptyne.⁷ Although this reaction was first postulated as proceeding through a cyclic transition state, it seems more likely that it involves an organo-zinc carbanion. Reduction of haloallenes gives the same proportion of products as does the reduction of the corresponding secondary propargyl halides.¹¹

An equilibrium mixture of propargyl halide and haloallene is produced by shaking a propargyl halide with cuprous halide, from which the haloallene can be fractionally distilled in fair yield.¹²

Lithium aluminum hydride can also be used to reduce propargyl halides to allenes. 3-Bromo-1-heptyne yielded a 9 to 1 ratio of 1,2-heptadiene and 1-heptyne, and 1,1-dimethylpropargyl chloride gave a 55% yield of dimethylallene and none of the acetylenic product, when treated with lithium aluminum hydride.⁹ A primary propargyl halide, however, gives very little, if any, allene. 1-Bromo-2-heptyne produced only 6% allene and 1-bromo-2-heneicosyne yielded only 2-heneicosyne when reduced with LiAlH_4 .¹³ Since the allene product is probably formed by an $\text{S}_{\text{N}}2'$ type attack by a hydride ion, whereas the acetylene is produced by a normal $\text{S}_{\text{N}}2$ attack, the relative predominance of the allene hydrocarbon in the products from the secondary halide compared with its absence in those from the primary halide may be due both to steric and inductive inhibition of $\text{S}_{\text{N}}2'$ type attack on the primary halide and of $\text{S}_{\text{N}}2$ attack on the secondary halide.



This reaction affords a convenient synthesis of allenes. Secondary and tertiary propargyl alcohols, readily obtainable by the condensation of acetylenes with aldehydes or ketones, are converted to allenes in good yield by treatment with HCl followed with LiAlH_4 . Thus 1,1-dimethylpropargyl alcohol was converted in 51% yield to 1,1-dimethylallene, and 1-methyl-1-ethylpropargyl alcohol (V) gave the corresponding allene (VI) in 49% yield. Isolation of the intermediate propargyl chlorides resulted, strangely, in a large decrease in yield for the overall reaction. 1-methyl-1-ethylpropargyl chloride (VII) gave only 3-methyl-2-pentene (VIII) when reduced with LiAlH_4 .¹⁴

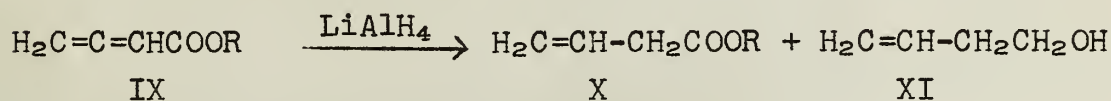


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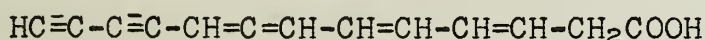
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Although refluxing VI in an ethereal solution of LiAlH_4 produced no trace of olefin (VIII), the hydrogenation of allenes with this reagent is not unknown. Jacobs has reported that 1-chloro-3-methyl-1,2-butadiene yielded isopentane when treated with an excess of LiAlH_4 , whereas the use of a somewhat smaller quantity of the hydride produced 3-methyl-1-butene.¹¹ Similarly, when buta-2,3-dienoic acid or its ethyl ester (IX) was reduced with LiAlH_4 at -20°C ., the product formed was largely vinylacetic acid (or its ester) (X). Some XI was formed also, but no trace of buta-1,2-diene-3-ol was found.¹⁵ This is quite unusual, as LiAlH_4 is generally considered to be unreactive toward carbon-carbon double bonds.

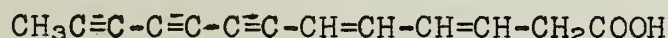


Interest in allenes and their reactions has been intensified by the recent elucidation of the structure of the antibiotic, mycomycin (XII). This compound is active against streptomycin-resistant strains of Mycobacterium tuberculosis, and is the first reported example of an optically active allene of natural origin. Mycomycin is unstable, and when treated with base undergoes a series of propargylic re-



XII

arrangements to isomycomycin (XIII).¹⁶



XIII

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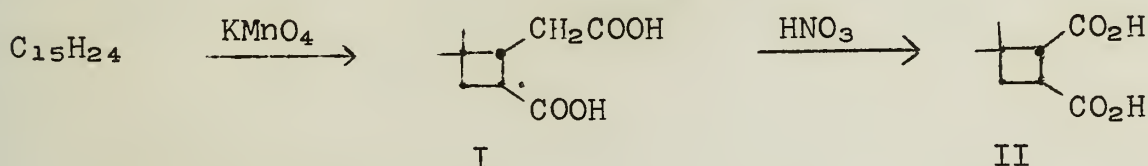
THE STRUCTURE OF CARYOPHYLLENE

Reported by R. Crawford

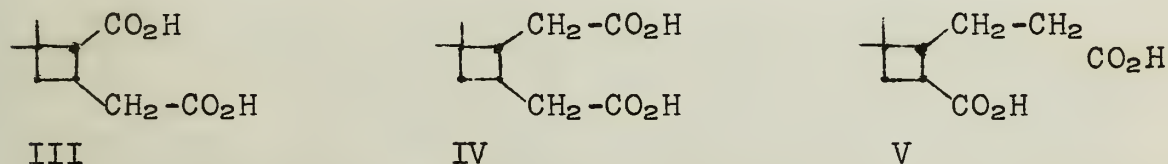
May 6, 1955

The sesquiterpene, caryophyllene, has long been known to be a bicyclic diene, but since it rearranges readily the determination of its structure has only recently been completed.¹

The fact that one of the rings is a cyclobutane derivative was not elucidated until 100 years after its discovery as a by-product in the processing of clove oil. Rydon², in 1935, was able to synthesize and resolve norcaryophyllenic acid II, which was identical with the compound obtained from the oxidation of caryophyllene.^{3,4}

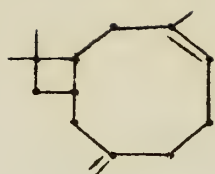


Ramage and Simonsen⁵ proved that caryophyllenic acid I was a structural homologue of norcaryophyllenic acid, but not until Dawson and Ramage⁶ precluded the structure III by synthesis was the structure I proven. Homocaryophyllenic acid was later identified by the same workers to have the less symmetrical structure V, by synthesis from optically active caryophyllenic acid⁷.

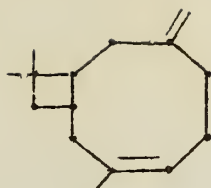


The ozonolysis experiment of Semmler and Meyer⁸ indicated the presence of an exocyclic methylene group, and a triply substituted double bond bearing one methyl group. Ruzicka and Wind⁹ showed that the ketone produced by ozonolysis of caryophyllene had an active methylene group.

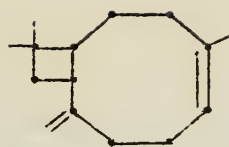
Treibs⁹ showed that oxidation of caryophyllene with hydrogen peroxide yields a mono-epoxide, which could be oxidized with permanganate to a solid, C_{14} epoxyketone. Isolation of this latter substance established that epoxidation had occurred on the more heavily substituted double bond. Sorm, Dolejs and Pliva¹⁰ carried out an intensive spectroscopic study of Treibs' ketone and other products of caryophyllene oxidation. From this they suggested that caryophyllene contained a nine-membered ring. From their spectroscopic data and chemical evidence available at that time the Czech group proposed the structures VI and VII for caryophyllene. Barton and Lindsey¹¹ produced sound chemical evidence in favor of the cyclononane ring.



VI



VII

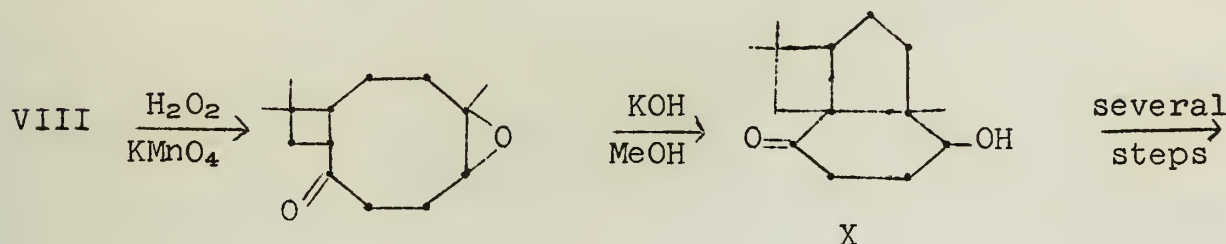


VIII

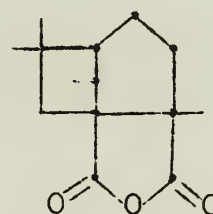


IX

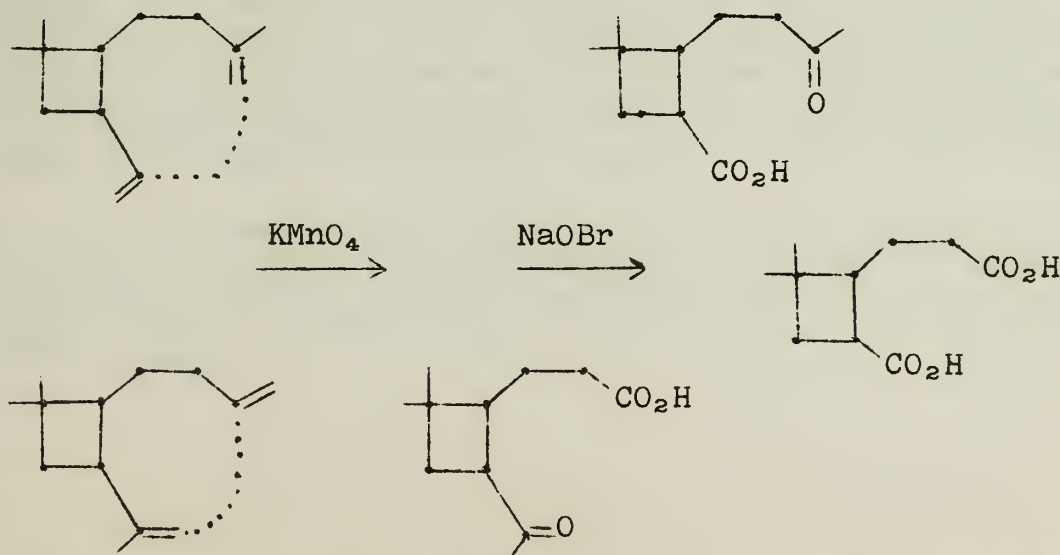
The scheme they proposed in proof of the cyclononane ring involves the formation of the tricyclic derivative X. The ease with which the dicarboxylic acid XI forms an anhydride coupled with infrared data identified it as a succinic acid derivative, and through mechanistic considerations they proposed VIII.



XI

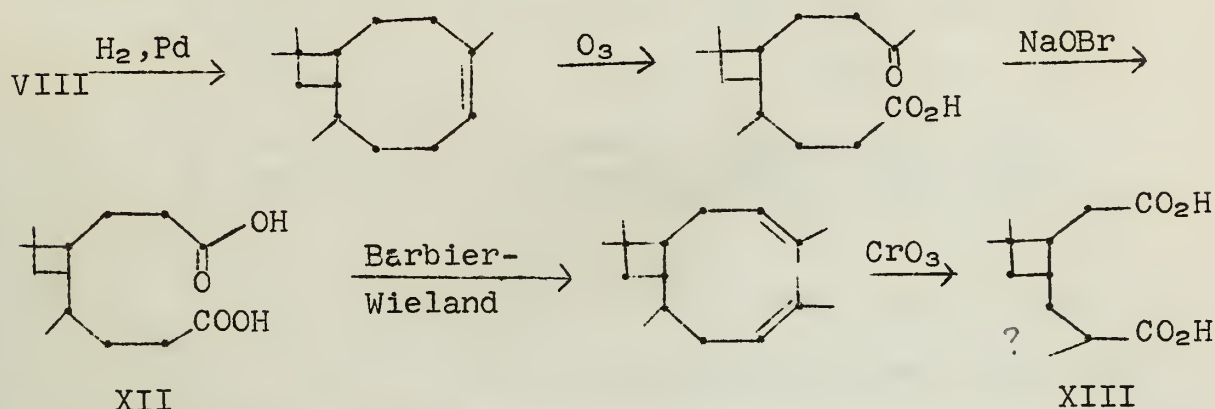


Dawson, Ramage and Wilson¹² from their experiments arrived at a similar conclusion regarding the skeletal structure of caryophyllene, but felt that IX best represented the structure. Direct oxidation of caryophyllene nitrosite by permanganate gave them three products, one of which was a keto-monocarboxylic acid which upon hypobromite oxidation yielded homocaryophyllenic acid.

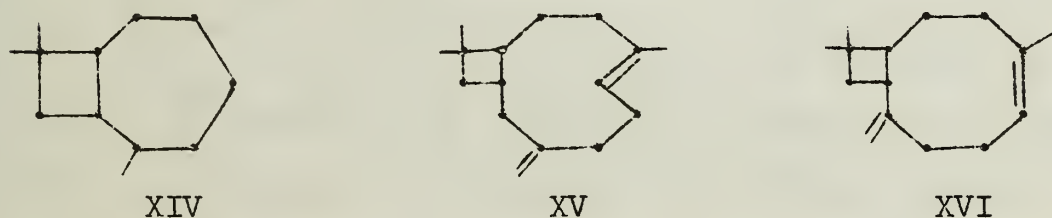


As a result of these findings and the identification homocaryophyllenic acid⁷ the structures VI and VII were no longer tenable.

Atwater and Reid¹³ were able to form a dihydro derivative which no longer gave formaldehyde on ozonolysis, but yielded a keto acid. The ozonolysis product when treated with hypobromite produced a C₁₄ dibasic acid XII, which on Barbier-Wieland oxidation XIII proved the existence of a methylene group adjacent to the ketone, thus eliminating structure IX.



Recently Dolejs and Sorm¹⁴ have given vigorous chemical proof to Barton's structure VIII by converting caryophyllene to a cycloheptane derivative XIV and carrying out an unequivocal synthesis of this derivative from homocaryophyllenic acid.



The geometrical isomer of caryophyllene, isocaryophyllene, has been known for a long time and yields different crystalline derivatives than does caryophyllene. Aebi, Barton and Lindsey¹⁵ established beyond reasonable doubt, by perphthalic acid oxidation studies¹⁶, and interconversions that caryophyllene possesses the strained trans arrangement XV, whereas isocaryophyllene is the more stable cis isomer XVI. Recent work by Ramage^{17,18} and coworkers has confirmed this relationship of the two isomers.

Barton and Nickon¹⁹ carried out a study on absolute configuration on derivatives of caryophyllene and by the use of molecular rotation rules²⁰ have related it to D-glyceraldehyde showing its true structure to be XV and not that of its mirror image.

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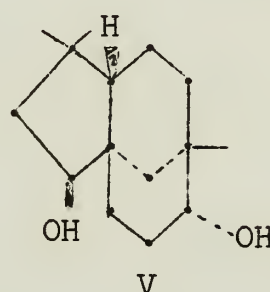
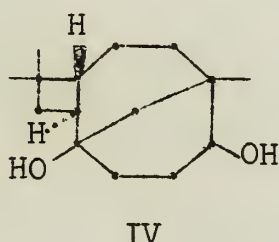
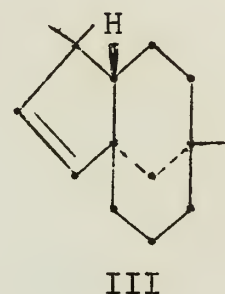
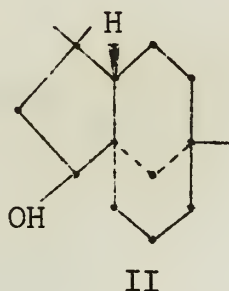
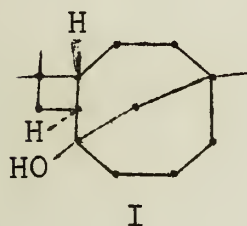
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REARRANGEMENTS OF THE CARYOPHYLLENES

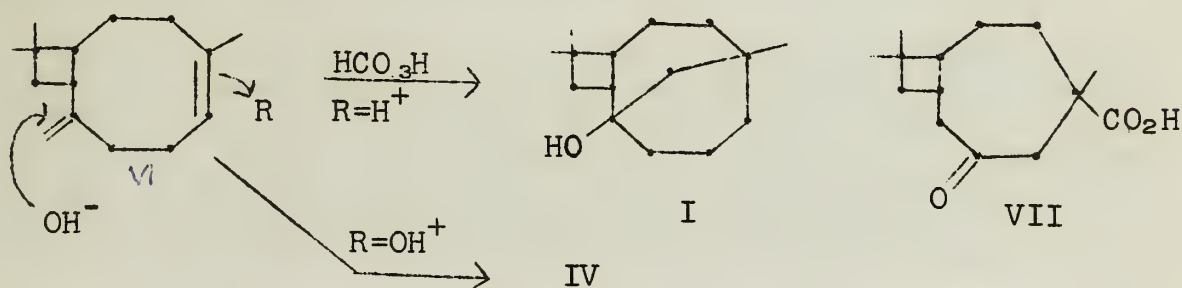
Reported by E. W. Cantrall

May 6, 1955

Introduction. Failure to recognize the ease with which both caryophyllene and isocaryophyllene undergo acid catalyzed rearrangements led early researchers to numerous erroneous structures for these substances and their products. Acid catalyzed rearrangements of the caryophyllenes give rise to five principal products:¹ β -caryophyllene alcohol (I), α -caryophyllene alcohol (II), clovene (III), and two glycols (IV and V).



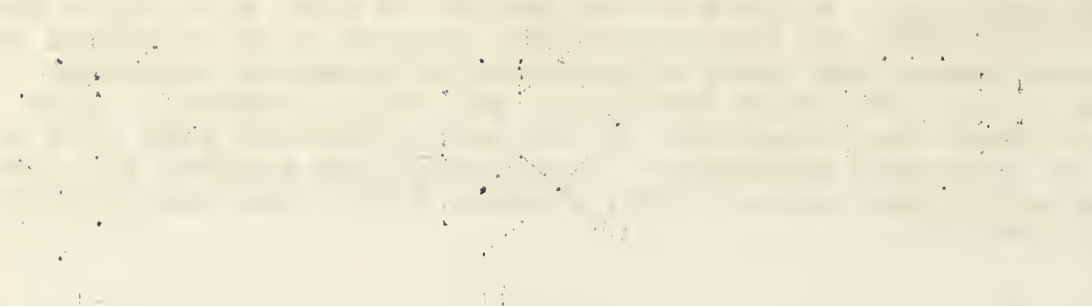
β -Caryophyllene Alcohol and Glycol. β -caryophyllene alcohol (I) and its corresponding glycol (IV) are readily obtained from iso-caryophyllene (VI) by acid catalyzed hydration with performic acid^{2,3}.



The glycol IV was degraded to the keto-acid VII by Barton, Bruun, and Lindsey¹ and was found to have the structure assigned.

Wallach and Walker⁴ noted that β -caryophyllene alcohol, when treated with various phosphorous pentahalides, gave rise to mono-substituted halides. Henderson, Robertson and Kerr³ observed that β -caryophyllene chloride, although resistant toward nucleophilic attack, could be converted to the corresponding acetate by treatment with NaOAc + HOAc. By chlorination of the mono-acetate of β -caryophyllene glycol (IV) and subsequent degradation to the same keto-acid (VII), it was

The first part of the paper is devoted to the study of the properties of the function $f(x)$ defined by the equation



It is shown that the function $f(x)$ is continuous and differentiable. The derivative of the function is given by the equation

The function $f(x)$ is also shown to be periodic with period 2π . The period of the function is determined by the value of the parameter a .

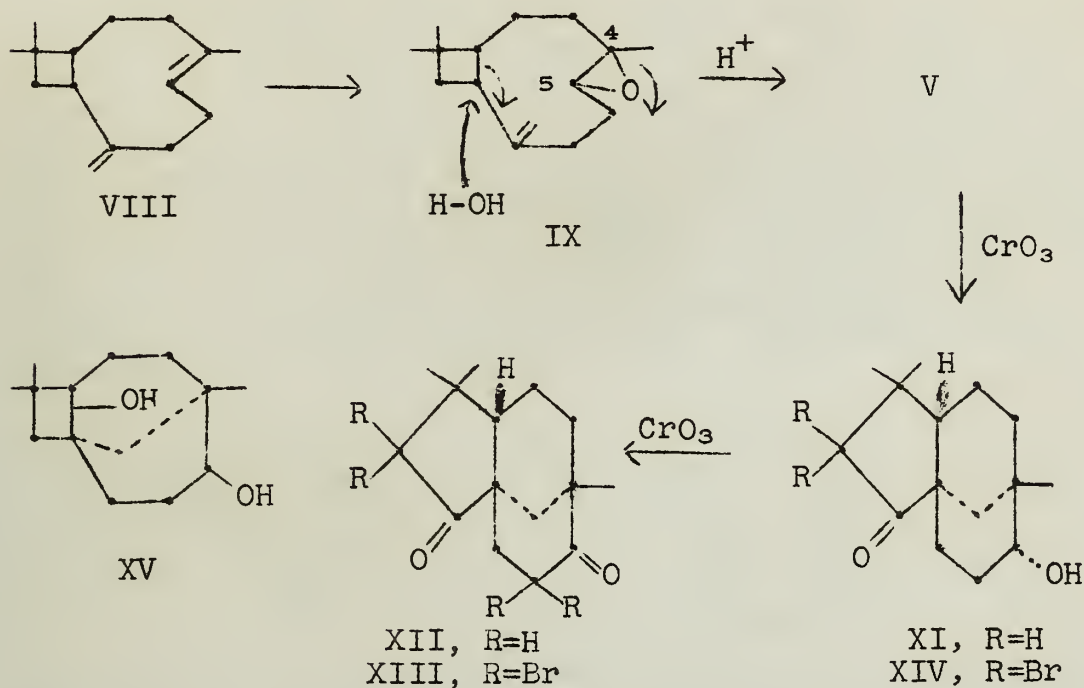


The function $f(x)$ is also shown to be bounded. The maximum value of the function is determined by the value of the parameter a .

In conclusion, it is shown that the function $f(x)$ is a periodic function with period 2π . The function is also shown to be continuous and differentiable. The derivative of the function is given by the equation

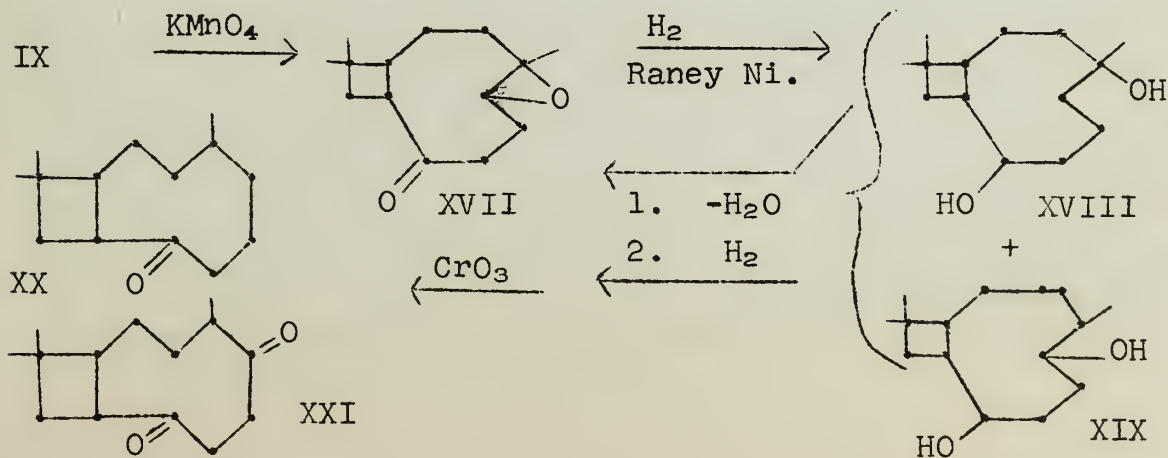
shown that replacement did occur without rearrangement and that β -caryophyllene alcohol has the structure I. X-ray work of Robertson and Todd¹² confirms the structure assigned β -caryophyllene alcohol chloride.

The Caryophyllene Oxides. Caryophyllene oxide IX, prepared with mono-perphthalic acid, undergoes rearrangement with acid to give the glycol (V),^{5,6} whose structure is deduced as follows:



The formation of the tetra-bromo derivative (XIII) gives evidence for the presence of at least four replaceable α -H's, and from the formation of the dibromo derivative (XIV), it is concluded that there are two replaceable α -H's adjacent to each carbonyl group. These data exclude XV as a possible structure for the glycol.

Upon re-examination of Treibs⁷ epoxy-ketone, Ramage and Whitehead⁸ concluded that both 3° and 2° alcohols were formed in opening the epoxide ring; the former gives rise to a mono-ketone from each of the three possible oxides of caryophyllene (1) and isocaryophyllene (2). In the isocaryophyllene series, opening of the epoxide ring goes with racemization at C-4, while the hindered caryophyllene series gives no racemization.

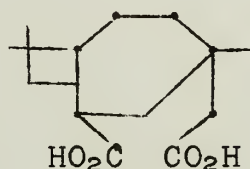


Clovene and β -Caryophyllene Alcohol. Clovene (III) has been prepared by several routes: by boiling β -caryophyllene alcohol (I) with H_3PO_4 ^{4,9}, by treatment of isocaryophyllene (VI) with glacial $\text{HOAc} + \text{H}_2\text{SO}_4$ ⁴, and by hydration of caryophyllene with Aschan's reagent ($\text{H}_2\text{SO}_4 + \text{Et}_2\text{O}$)^{10,11}. Lutz and Reid's treatment of caryophyllene with Aschan's reagent led to a mixture of (I), crude (III), small amounts of (II), and a new product $\text{C}_{15}\text{H}_{26}\text{O}$.

Wallach and Walker,⁴ upon treatment of (I) with P_2O_5 , obtained a liquid hydrocarbon, $\text{C}_{15}\text{H}_{24}$, which they assumed to be clovene because of its similarity to the isomerization product of (I); however, they were unable to regenerate the β -alcohol, from which they concluded that the hydroxyl group was located at a bridgehead carbon and that rearrangement was concomitant with dehydration. Lutz and Reid¹¹ repeated the P_2O_5 dehydration and obtained a hydrocarbon resembling clovene in boiling point and index of refraction but which was markedly different in rotation, IR spectrum, and chemical behavior. The product was called pseudoclovene and tentatively assigned structure XXII. Oxidation of XXII gave pseudoclovenic acid (XXIII).



XXII



XXIII

Lutz and Reid also found that treatment of I with Aschan's Reagent or with 20% H_2SO_4 for 4-1/2 hours gave back starting material; however, treatment of I with conc. H_2SO_4 in Et_2O at 75° for one hour afforded a mixture consisting of a saturated hydrocarbon (75%) and an unsaturated hydrocarbon (25%). Oxidation of the mixture gave I. Thus in spite of the apparent close relationship between I and clovene, it is not possible to effect the transformation in the laboratory.

The Stereochemistry of the Tricyclic Products. Barton, et. al.,¹³ have shown that the acid catalyzed rearrangements of caryophyllene and caryophyllene oxide give rise to two different glycols. The glycol V is closely related to the structure for clovene.^{1,10,11,14,15}

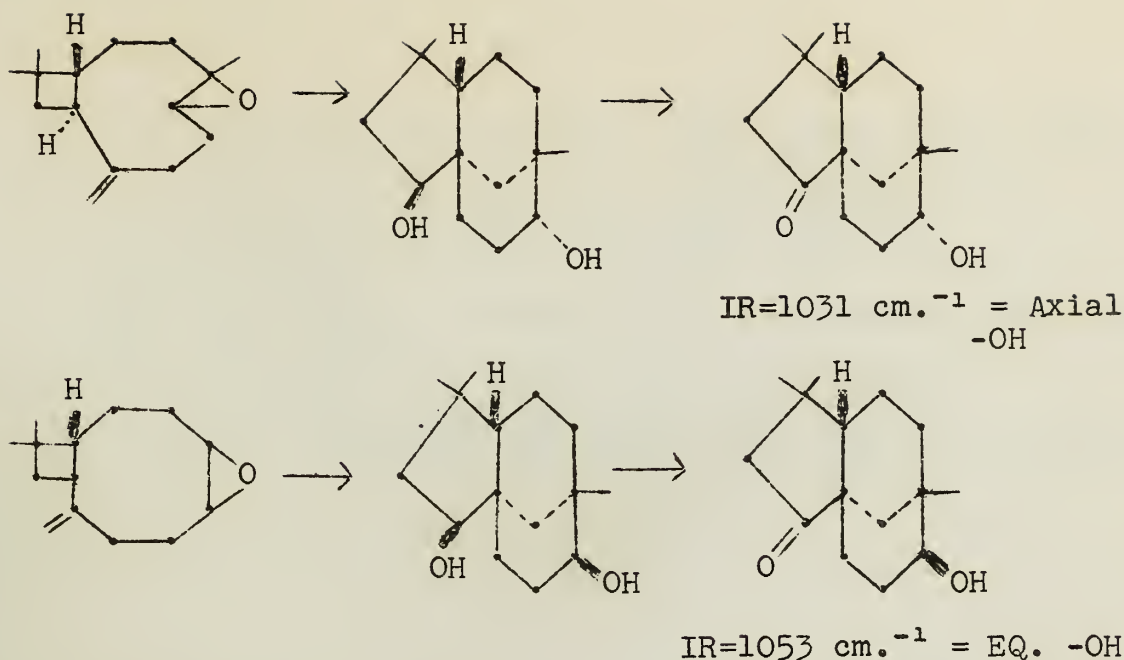
It is now recognized that acid catalyzed dehydration of (I) does not give clovene (III) as would be anticipated if the methylene bridge had the same configuration in both cases.^{11,16} If I does not give III, then IV cannot be an intermediate in the formation of V^{1,15}. It is then immediately obvious that I and (III) are of different stereochemical families. If the methylene bridge in V is α , it must have come from the opening of the β -oxide with inversion. The 9-hydroxyl is then α and axial, and the epimeric β -hydroxyl group derived from the isocaryophyllene oxide must be equatorial. Barton¹⁷ confirms this deduction with his observations that 9- α -hydroxyl derivatives are more easily oxidized than the 9- β compounds.

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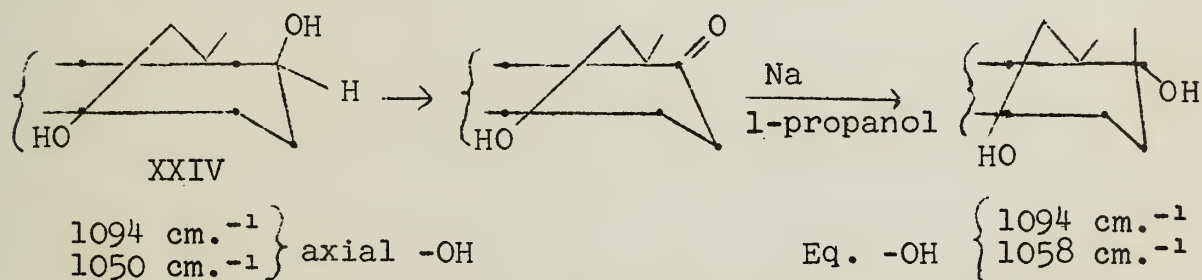
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(continued)



The glycol IV isolated as a by-product in the preparation of caryophyllene oxide has a β -methylene bridge. To insure trans electrophilic addition, it must be produced by α attack by OH^+ on the endocyclic double bond; hence, the configuration of the secondary hydroxyl must be β (note the apparent inversion). Robertson and Todd¹² have shown via X-ray studies that ring C of XXIV adopts the more stable chair form. The secondary hydroxyl must then be β -axial. That it is has been confirmed experimentally.¹³



A review of the work on the rearrangements of the caryophyllenes up until early 1954 is available.¹⁸

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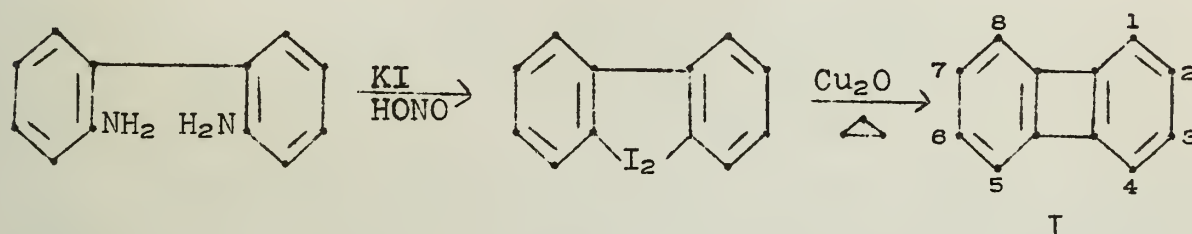
DERIVATIVES OF CYCLOBUTADIENE

Reported by G. W. Griffin

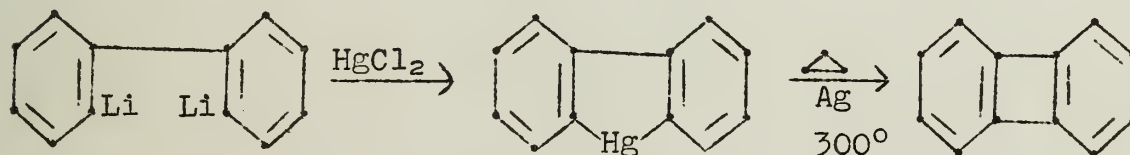
May 13, 1955

Although many attempts to prepare cyclobutadiene are recorded,¹ this hydrocarbon and its simple derivatives have long eluded synthesis. Several compounds which contain a four-membered ring fused to an aromatic nucleus are known, however. Such compounds can be regarded as derivatives of the unknown cyclobutadiene.

Biphenylene (I), the simplest dibenzocyclobutadiene, was first synthesized by Lothrop in 1941.^{2,3} He employed the following sequence of reactions which afforded a 15% yield of the yellow hydrocarbon.



A superior synthetic route to biphenylene has recently been disclosed by Wittig and Herwig.⁴ Yields as high as 54% are reported:



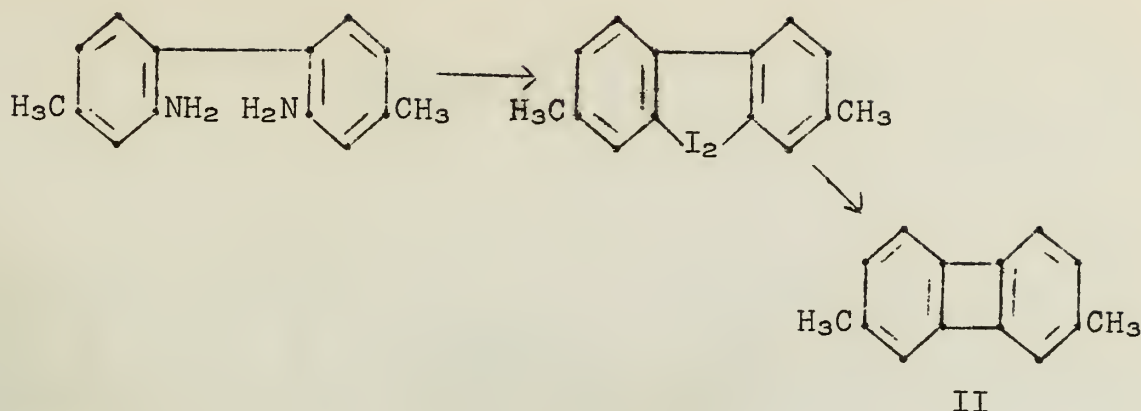
The chemical properties of biphenylene have not been investigated extensively. Hydrogenation in the presence of hot metallic copper or Raney Nickel results in cleavage of the four-membered ring and formation of biphenyl.^{2,3,5} The principal product of chromic acid oxidation is phthalic acid which establishes the presence of ortho substitution.² Acetylation of biphenylene in the Friedel-Crafts manner is found to occur chiefly at the 2 position. This reaction constitutes the only significant example of electrophilic monosubstitution of the biphenylene nucleus.⁵

Considerable controversy has arisen over the question of whether I or III represents the true structure of the hydrocarbon obtained by Lothrop. As chemical evidence in favor of the symmetrical structure I, Lothrop cites the fact that 2,7-dimethylbiphenylene (II) can be prepared by either of the following routes.²

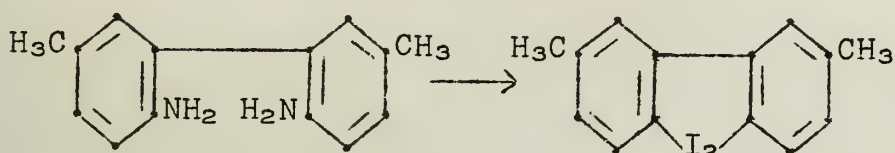
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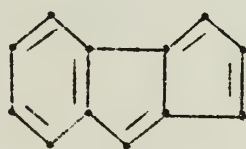
Path a



Path b



It has been suggested by Baker,⁶ however, that a rearrangement of the transiently formed biphenylene to the more stable benzopentalene (III) occurs. This postulation is in harmony with the experimental observation that either path (a) or (b)

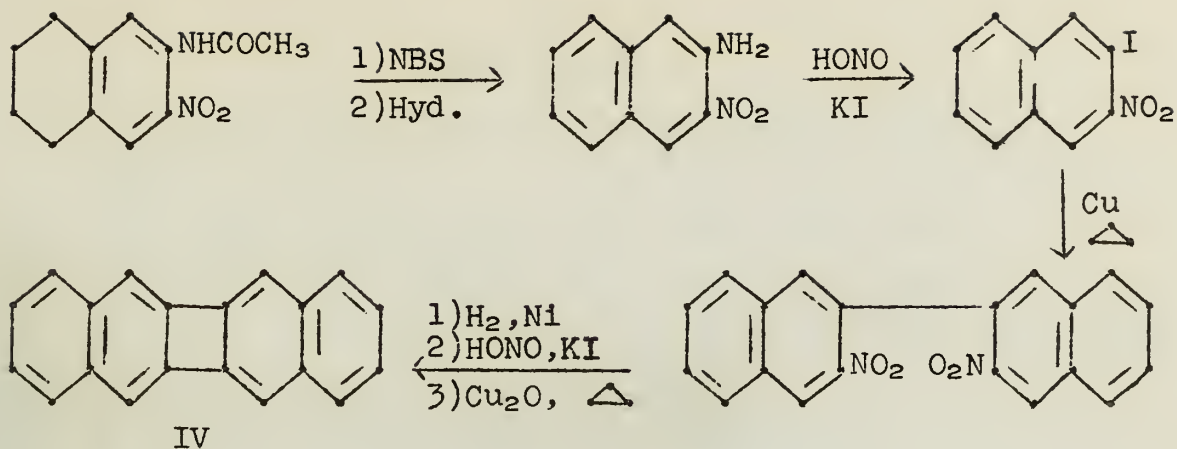


III

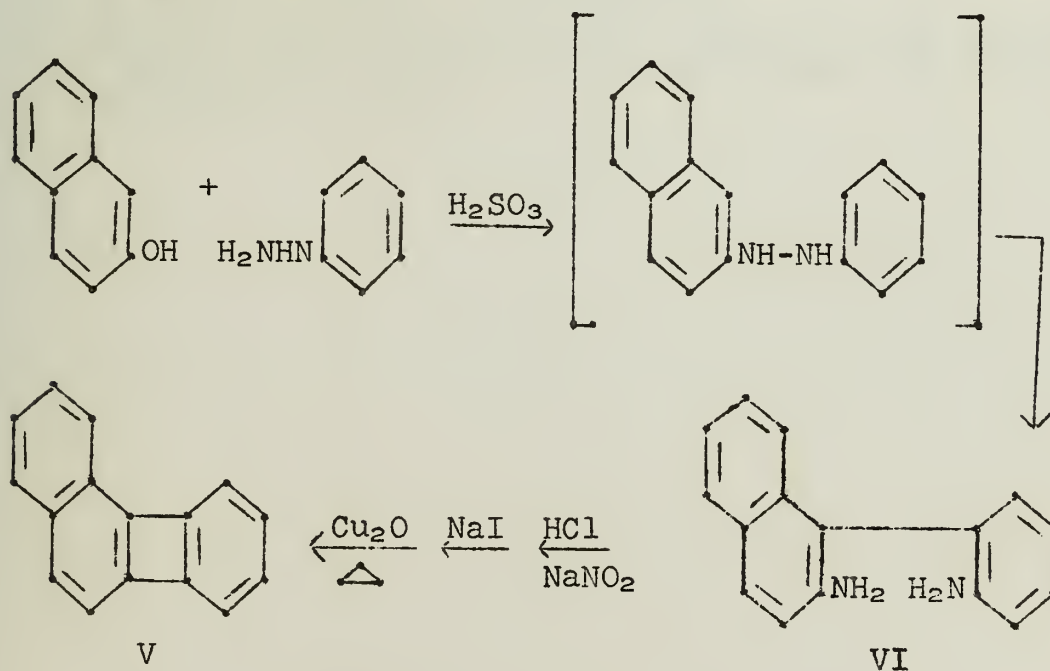
leads to the same hydrocarbon since the rearrangement occurs subsequent to formation of II. The formulation III is further supported by calculations of strain and resonance energies.⁷ The ultraviolet absorption spectrum of the hydrocarbon likewise is in closer agreement with that calculated for structure III.⁸ Electron diffraction investigations⁹ and X-ray crystal analysis,¹⁰ however, give conclusive evidence that I represents the correct structure for the hydrocarbon.

2,3-Binaphthylene (IV) was recently prepared by Curtis and Viswanath¹² who used essentially the same sequence of reactions employed by Lothrop in the synthesis of biphenylene.

The ultraviolet absorption spectrum of 2,3-binaphthylene is similar to that of biphenylene.¹³ Hydrogenolysis of this hydrocarbon in ethanol in the presence of Raney Nickel converts it to 2,2'-binaphthyl.¹² The melting point of 2,3-binaphthylene ($376 \pm 2^\circ$) is considerably higher than that of biphenylene ($109-10^\circ$). Curtis¹³ attributes this fact to a reduction in the cyclobutadienoid character of the four-membered ring of 2,3-binaphthylene.



The most recent dibenzocyclobutadiene to be prepared is 1,2-benzobiphenylene (V).¹⁴ In this synthesis use is made of the Bucherer reaction for the preparation of the diamine VI which is subsequently tetrazotized, treated with NaI and pyrolyzed to produce VI.



The pure hydrocarbon was isolated by a process involving formation of its 2,4,7-trinitrofluorenone complex. Decomposition of this complex and isolation of the pure hydrocarbon were effected by adsorption chromatography.¹⁴ The structure V was confirmed by its reduction to a mixture of α -phenyl- and β -phenylnaphthalene in yields of 50 and 21% respectively.

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REACTIONS WITH NITROSODISULFONATE

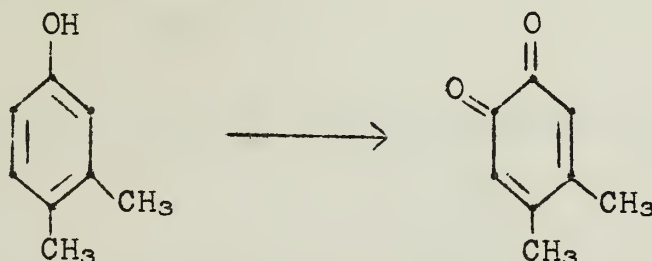
Reported by J. J. Miller

May 13, 1955

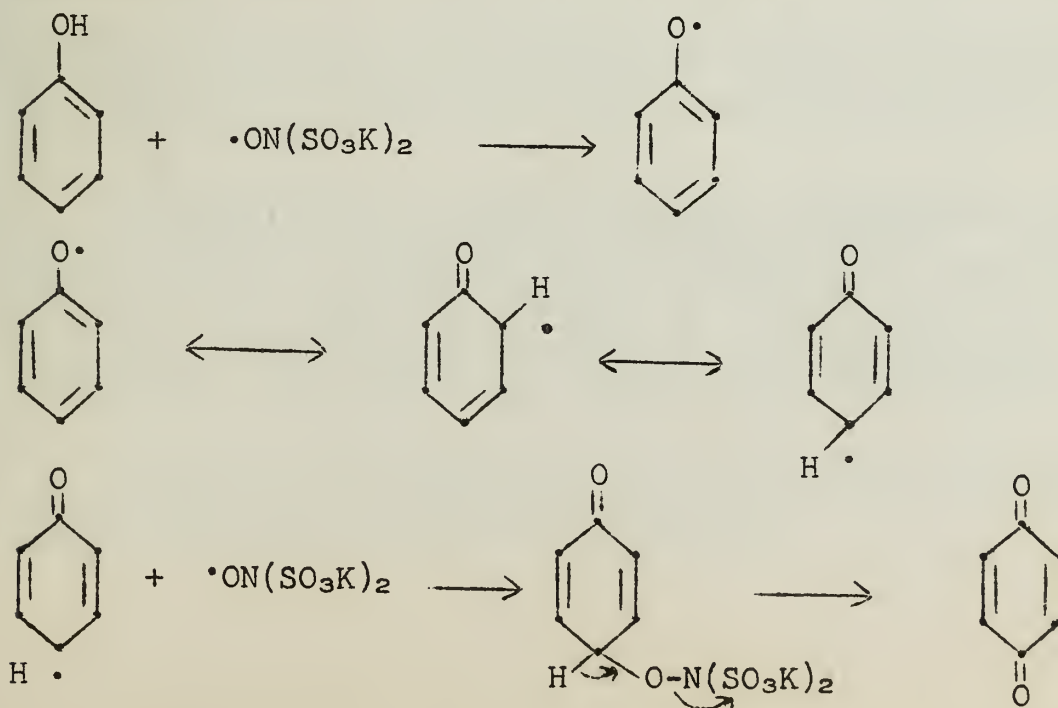
Potassium nitrosodisulfonate, $\cdot\text{ON}(\text{SO}_3\text{K})_2$, was first described by Fremy in 1845.¹ Only in recent years, however, has it found use as a reagent for synthetic work. The free radical nature of this material is demonstrated by its paramagnetic properties and the violet color of its solutions.

The ability of nitrosodisulfonate to function as an oxidizing agent was first observed when a small amount of nitrosobenzene was isolated from the reaction of aniline and the reagent.² Application of this reagent to the oxidation of phenols has met with great success; in fact, the reaction has been found to be quite general.^{3,4,5} Hydroquinone and phenol, upon treatment with nitrosodisulfonate, both yield 1,4-benzoquinone. If only half the theoretical amount of the reagent is employed, molecular complexes of the quinone and the phenol result.

Quinone formation is not limited to phenols with a free para position; ortho quinones result from the oxidation of para-substituted phenols. For example, 3,4-dimethylphenol is oxidized to an ortho quinone according to the following equation:



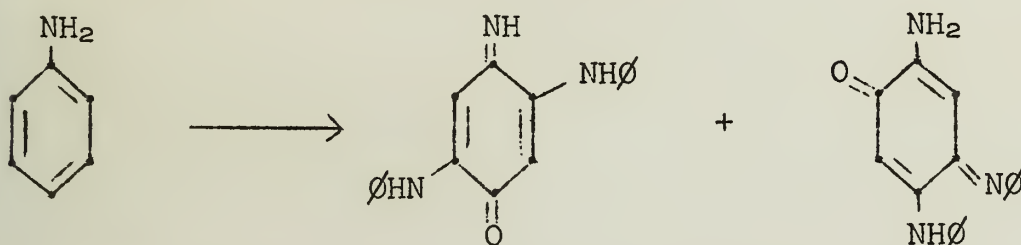
There is a great deal of similarity between this reaction and the Elbs persulfate oxidation.⁶ The proposed mechanisms follow the same general course.



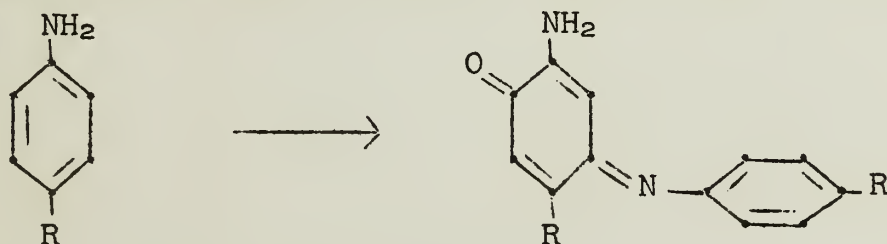
Although electron withdrawing groups such as $-Cl$ and $-NO_2$ aid the Elbs persulfate reaction, oxidations with potassium nitrosodisulfonate do not proceed when the electron density of the ring is reduced by such functions. Phenol oxidation has been successfully extended to naphthols.⁷

Potassium nitrosodisulfonate has been found to effect decarboxylations of *p*-hydroxybenzoic acids to give the corresponding para quinones. Even those acids which are unsubstituted in the positions ortho to the phenol group undergo decarboxylation rather than ortho quinone formation.

Primary aromatic amines react with the reagent to produce quinone imines as the major products.⁸ As mentioned, nitrosobenzene is a minor product of the oxidation of aniline. Three moles of aniline are dehydrogenatively coupled and an oxygen atom is introduced.



Para-substituted alkyl or alkoxy aromatic amines also couple.



Indole quinones and 5-hydroxyindoles arise from the reaction of dihydroindoles with the reagent.⁹ If the carbon atom in the 3-position is quaternary, the reaction stops at the indolenine stage.¹⁰

Dehydrogenation of hydrazobenzene to azobenzene occurs readily under the influence of nitrosodisulfonate. Similar dehydrogenation of phenylhydrazine should give a diazonium compound, and indeed the presence of phenyl diazonium ion in the reaction has been established by its coupling with β -naphthol. Acid hydrazides likewise are dehydrogenated and subsequently oxidized to the corresponding acids and nitrogen.¹¹

Aldehyde phenylhydrazones are oxidized to acid phenylhydrazides by the reagent, but because of steric factors ketone phenylhydrazones are not affected.

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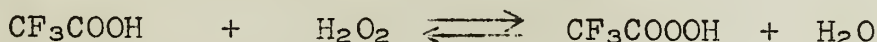
PEROXYTRIFLUOROACETIC ACID--A NEW SYNTHETIC TOOL

Reported by Leslie M. Werbel

May 20, 1955

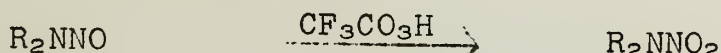
Organic peracids have been known for many years, and the advantages of their use in various oxidative procedures widely recognized¹. Rarely, however, has a peracid, or for that matter any type of oxidative reagent come upon the scene with the multiplicity of valuable applications ascribed to the discovery of peroxytrifluoroacetic acid recently reported by Emmons²⁻⁶.

It was first noted late in 1953 that a solution of hydrogen peroxide in trifluoroacetic acid had rather potent ability as an oxidizing agent, and this was quite reasonably attributed to the formation of the corresponding peracid.



Oxidation of Nitrosamines to Nitramines³

The preparation of nitramines, which are of some interest as explosives, has in the past been carried out through rather laborious procedures, as for example through the alkyl amides⁷ or through nitration of chloroamines⁸. It has now been shown that peroxytrifluoroacetic acid will convert nitrosamines, now readily available from nitrosation of the corresponding amines, to high purity nitramines in excellent yields.

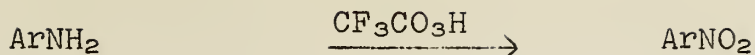


The preferred method of operation is to prepare the peracid from 90% H₂O₂ and trifluoroacetic anhydride in methylene chloride with cooling, and then to add the nitrosamine gradually. After refluxing for short times the products are easily isolable by distillation.

Oxidation of Anilines to Nitrobenzenes⁴

This use of the reagent is probably one of its most important applications. The introduction of nitro groups into aromatic systems sensitive to direct nitration techniques has long been a preparative problem, and many indirect methods have found their way into the literature⁹. Most of these involve specific cases wherein the starting materials are so difficult to obtain as to make the methods of little value. The most important general methods in use involve replacement of the diazo group by nitro through use of various catalysts and diazo salts such as the cobaltinitrites¹⁰ sulfates¹¹ and the borotri-fluorides¹². Some mention has also been made of the use of peracetic acid to effect this conversion^{13,14}, but yields have been low and formation of substantial amounts of azoxy compounds limited the method.

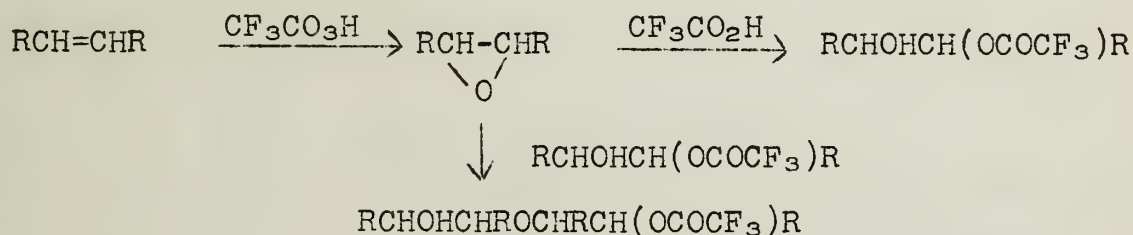
Peroxytrifluoroacetic acid converts a wide variety of anilines to the corresponding nitro compounds, smoothly, in high yield and no indication of contaminants such as azoxy compounds was noted.



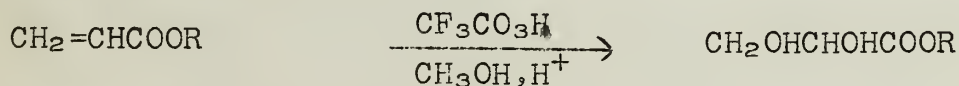
Although this reagent is well suited for preparation of many difficult to obtain nitro compounds, its application is unfortunately not completely general. Aromatic nuclei containing electron donating groups are attacked by the reagent, and the corresponding nitro compounds cannot be obtained in this manner. Thus *p*-anisidine yields no *p*-nitroanisole, and β -naphthylamine results in an intractable mass.

The Hydroxylation of Olefins⁵

One of the most important methods of preparing alpha glycols from olefins involves the use of aliphatic peracids¹⁵. Peroxytrifluoroacetic acid has been found an excellent reagent for effecting this transformation. The reagent seems more reactive than performic acid and is particularly attractive in the synthesis of water soluble alpha glycols. The products first formed are the hydroxy trifluoroacetates, which are easily converted to the glycols with methanolic HCl. To avoid contamination with high boiling ethers formed from the epoxide and the hydroxytrifluoroacetates, triethylammonium trifluoroacetate is added thus effectively increasing the trifluoroacetate concentration.



The method was particularly applicable for syntheses of glycerates and 1,2-dihydroxyisobutyrate. In these cases a sulfonic acid resin was used in place of HCl in the hydrolyses to avoid transesterification.

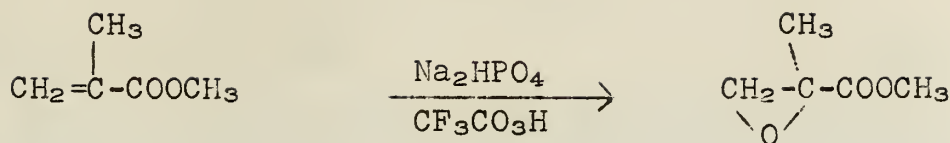


The Epoxidation of Olefins⁶

The reagent was found well suited for the preparation of epoxides from olefins and negatively substituted olefins. It is especially advantageous in the case of long chain terminal olefins which with other peracids gave low yields and involved lengthy reaction times¹⁶.

The success of the reaction depends upon the use of a buffer of Na_2CO_3 or Na_2HPO_4 , (with the negatively substituted olefins), to remove any CF_3COOH formed and thus prevent opening of the epoxide.

Use of peroxytrifluoroacetic acid offers advantages over perbenzoic acid, which up to this time has been the peracid of choice for this procedure, with respect to yield, purity of product, and ease of reagent preparation.



Conversion of Ketones to Esters^{17,20}

Peroxytrifluoroacetic acid has also been applied to the Baeyer Villiger type ketone oxidation. Although peracetic, perbenzoic and Caro's acid have been used in this connection most of the work has concerned alicyclic, aralkyl, and aromatic ketones. It has now been shown that the new reagent in the presence of Na_2HPO_4 converts aliphatic ketones to esters smoothly and rapidly in addition to effecting ring enlargement of cyclopentanone and cyclohexanone. The latter proceeds in better yield than when conducted with perbenzoic acid^{18,19} and avoids the lengthy preparation of that reagent. Of especial interest is the conversion of methyl cyclopropyl ketone to cyclopropyl acetate in 53% yield. This reaction did not take place with perbenzoic acid.

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STRUCTURE OF RESERPINE

Reported by R. J. Leary

May 20, 1955

Extracts of the Indian plant *Rauwolfia serpentina* Benth have been used for some time in India for the treatment of hypertension and other clinical conditions. Recently a crystalline alkaloid, reserpine¹, has been isolated from this plant which possesses pronounced sedative and hypotensive properties^{12,15}. Since then, its isolation from other *Rauwolfia* species has been reported^{6,7,13,14}.

Reserpine has the empirical formula $C_{30}H_{40}O_9N_2$. It contains 6 methoxyl groups and shows an absence of $N-CH_3$ and $C-CH_3$ ^{2,4,5}.

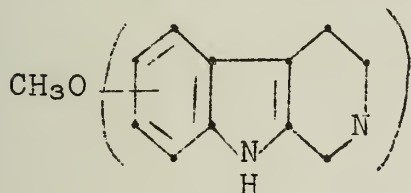
Reserpine I yields three fragments upon hydrolysis with alcoholic sodium hydroxide, reserpic acid II 3,4,5-trimethoxybenzoic acid^{2,4,5} and methanol. Reserpic acid ($C_{22}H_{28}O_5N_2$) upon esterification yields methyl reserpate IV^{2,4}, an hydroxy ester.

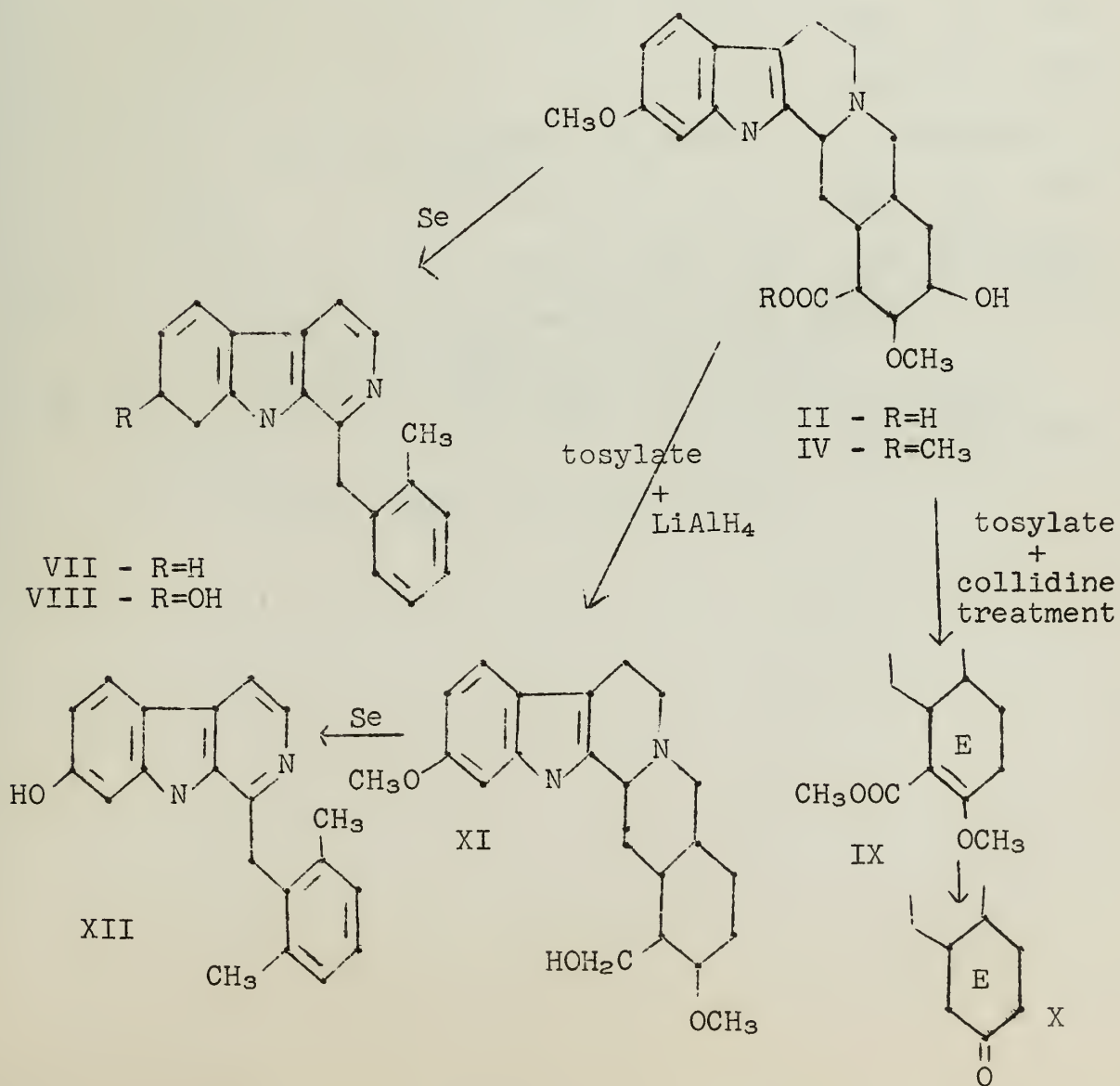
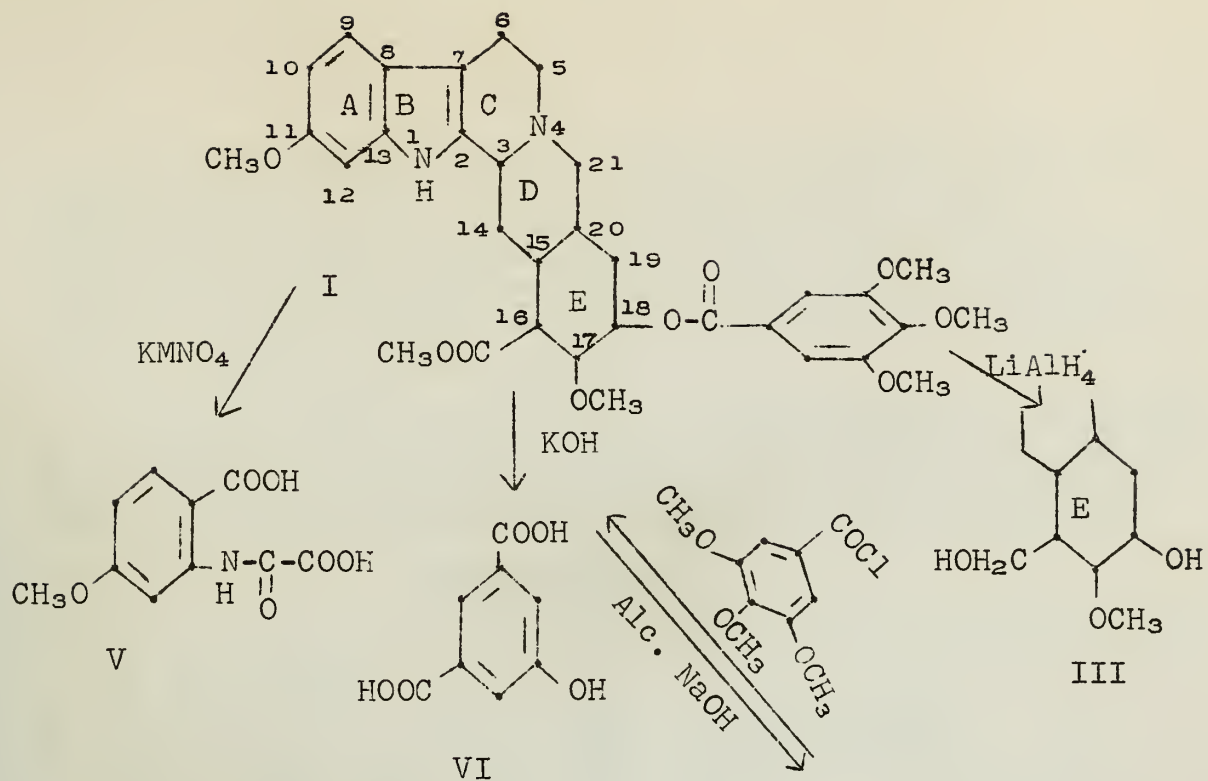
Reduction of reserpine with $LiAlH_4$ ⁵ yields reserpic alcohol III and 3,4,5-trimethoxy benzyl alcohol. Spectral evidence indicates that reserpic acid contains a monomethoxylated tetrahydro β -carboline system. Oxidation of reserpic acid with $KMnO_4$ yielded 4-methoxy-N-oxalylanthranilic acid³ V and KOH fusion yielded 5-hydroxyisophthalic acid VI. The isolation of the isophthalic acid derivative makes it appear likely that reserpic acid is a derivative of yohimbane.

Further proof for the presence of a yohimbane skeleton was obtained from the selenium dehydrogenation of reserpic acid⁹ in which yobyryne VII and hydroxy-yobyryne VIII were isolated. Upon this basis the structure II was assigned to reserpic acid. The positions for the carboxyl and methoxyl groups were chosen as position 16 and 17 respectively purely on a biogentic basis. The hydroxyl group was assigned position 18 since reserpic acid very easily forms a lactone which is characterized by I.R. as a γ -lactone (1773 cm.^{-1}) and also because of the formation of the symmetrical hydroxyisophthalic acid upon KOH fusion of reserpic acid.

In order to determine the position of the substituents on ring E¹⁰ the tosylate of methyl reserpate was prepared. This was then detosylated with collidine to give methyl anhydroreserpate IX which upon acid hydrolysis and simultaneous decarboxylation gave reserpone X.

Although these three reactions indicate with some degree of certainty the relative position of the ring E substituents of reserpic acid, it was essential that at least one of them be located definitely to serve as a point of reference. The carboxyl group was chosen to serve this purpose.





In the selenium dehydrogenation of reserpine acid the carboxyl was lost but if the carboxyl was converted to a hydroxymethyl XI group prior to dehydrogenation then a methyl substituted 7-hydroxyxybyrine XII could be isolated. The entire carbon skeleton of ring E was thereby retained and the position of the methyl group indicates the position of the original carboxyl group.

The structure of the methyl 7-hydroxyxybyrine was proven by synthesis, thereby establishing the structure of reserpine as I. Recently the stereochemistry of reserpine¹¹ has been shown to be configurationally similar to epi- α -yohimbane.

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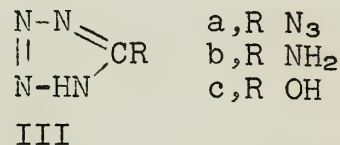
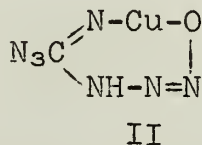
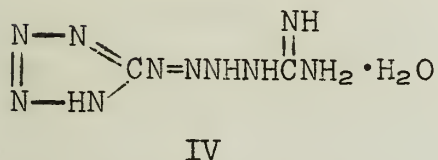
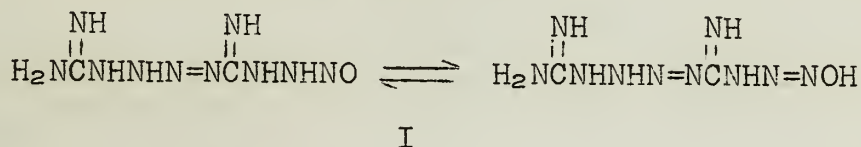
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THE STRUCTURE OF TETRACENE

Reported by Melbert Peterson

May 20, 1955

While studying the chemistry of nitroguanidine and its derivatives, Hofmann and Roth¹, on treating aminoguanidinium nitrate with sodium nitrite in neutral solution, isolated a white crystalline solid, $C_2H_8N_{10}O$ (I). This solid on hydrolysis in strong base gave ammonia, cyanamide and β -nitrosoaminoguanyl azide, which was isolated as the copper salt II. The azide, according to Hofmann, was converted by acid to 5-azidotetrazole (IIIa). Heating of I in dilute sulfuric acid gave nitrogen (2 moles), 5-aminotetrazole (IIIb), urea, hydrazine and cyanogen. Furthermore, in the presence of β -naphthol, an acidified suspension of I in water gave an azo dye, which indicated to Hofmann the presence of a nitrosoamine function². On the basis of this evidence the structure I, 1-guanyl-4-nitrosoaminoguanyl isotetrazene, (or that of the tautomeric diazonium hydroxide) was assigned to the compound. The name has since been shortened to Tetracene by ordnance investigators.



The possibility of a tetrazole ring in I was rejected by the early workers because of apparent differences between I and 1-(5'tetrazoyl)-4-guanyl tetrazene (IV), which was obtained from tetrazolediazonium chloride and aminoguanidinium nitrate². Significantly, however, the same products were obtained on alkaline hydrolysis of both I and IV.

Because of a lack of conclusive evidence excluding the tetrazole ring from Tetracene, and since Tetracene has practical application as a replacement for, or a sensitizer of, other primary explosives such as mercuric fulminate or lead azide³, the structure has recently been reinvestigated by Horwitz, Lieber and Patinkin⁴. Preliminary work showed that Tetracene could be recrystallized from nitric acid without decomposition, whereas known nitrosohydrazines are stable only at low temperatures and lose water on acid or alkaline treatment to give azides⁵.

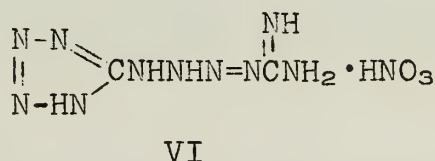
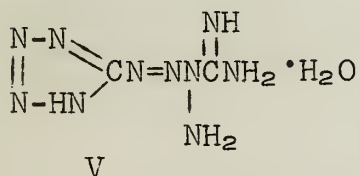
On degradation of Tetracene with barium hydroxide, the only organic solid obtainable was 5-azidotetrazole⁴. In the degradation, one mole of ammonia was evolved rapidly, while another mole appeared on longer treatment with base. Since nitrosohydrazines are unstable in base and acid it would seem likely that the product obtained by Hofmann probably cyclized before acid was added or, on the other hand, that the tetrazole ring itself is present in Tetracene.

Reduction of I with sodium and liquid ammonia gave 5-aminotetrazole. Lieber and Levering⁶ found that 5-azido-tetrazole could be readily reduced to 5-aminotetrazole with H₂S or HI. Thus, it appears that the azido compound is first produced by action of the ammonia and then is reduced to the amine.

First direct experimental evidence for the presence of the aminoguanidine group was obtained by acetylation studies. I with acetic anhydride and a trace of pyridine gave an isomeric mixture of diacetyl derivatives of 3-methyl-5-amino-1,2,4-triazole similar to those obtained on acetylation of aminoguanidinium nitrate and 3-methyl-5-amino-1,2,4-triazole⁴.

Reilly and co-workers⁷ investigated the azo dye formed by Tetracene and β-naphthol and clearly established the presence of a tetrazole ring in the compound. The ring was postulated to have been formed by a prior cyclization reaction in acid, giving the tetrazolediazonium hydroxide, which would then undergo coupling. Horwitz and co-workers point out, however, that the formation of 5-hydroxytetrazole and rapid liberation of nitrogen suggest the presence of an azotetrazole function in Tetracene. Furthermore, it is a characteristic reaction of substituted unsymmetrical tetrazenes to breakdown to a hydrazine and a diazonium compound in acid⁸.

Treatment of I with 15% sulfuric acid resulted in evolution of two moles of nitrogen. Addition of benzaldehyde and sodium nitrate to the acid hydrolysate gave a precipitate of benzalaminoguanidinium nitrate in 45% yield. 5-Hydroxytetrazole (IIIc) was isolated from the filtrate. Since all of the nitrogen present in I is accounted for in the products of acid degradation, Horwitz et.al. propose either IV or V as the correct structure of Tetracene. However, since V would not give the azide obtained on treatment with alkali, it has been discarded. Most convincing evidence for IV comes from the fact that addition of aminoguanidinium nitrate to a neutral solution of tetrazolediazonium chloride produced a white solid whose properties were identical with those of Tetracene.

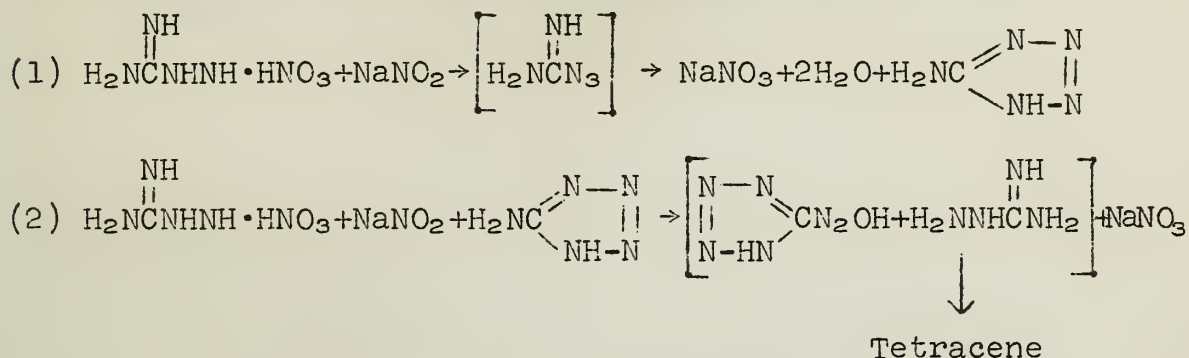


Since IV is identical with that proposed by Hofmann for the product obtained by coupling tetrazolediazonium chloride and aminoguanidinium nitrate, this reaction was reinvestigated by Horwitz et.al.⁴. It was found that the product obtained from the reaction varied with the pH of the diazo salt solution. On partial neutralization with sodium acetate, the product obtained had the empirical formula C₂H₇N₁₁O₃, and to which structure VI was assigned.

It is reported in the literature^{11,12,13} that, in the presence of mineral acid, substituted phenylhydrazines and

benzene diazonium chlorides couple to give unstable 1,4-disubstituted tetrazenes which break up, producing two azides and two amines; indicating that the tetrazenes are tautomeric. However, IV and VI, on degradation, each give one amine and one azide. Attempts at interconversion of the two have all been unsuccessful.

Since Tetracene can be synthesized by coupling tetrazolediazonium chloride and aminoguanidinium nitrate, Horwitz et.al. proposed the existence of these compounds as intermediates in Hofmann's original procedure. Furthermore, Hofmann's method provides the best yield of Tetracene (88%). Thus, it was of some interest to study the mechanism of this procedure, and the following scheme has been proposed by Horwitz, Lieber and Patinkin⁴:



The action of nitrous acid on aminoguanidine to give the azide and the subsequent cyclization in neutral solution (1) are well known reactions¹⁴. They have been used to explain the formation of 1,3-bis-5-tetrazoletriazene from sodium nitrite in acetic acid¹⁵. Reaction (2) was carried out independently and a precipitate formed immediately, whereas, in the normal procedure, several hours elapse before precipitation occurs. Reaction (1) must be the slow, or rate determining step, since if it were rapid, complete conversion to the guanyl azide would be expected, and as a result, (2) would not take place. Increase of the yield of Tetracene to 94% by using two moles of aminoguanidinium nitrate per mole of sodium nitrite further substantiates this hypothesis. From these observations the proposed steps appear to represent a reasonable mechanism for formation of Tetracene by the method.

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